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PAIN *

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EXPERIMENTAL PRODUCTION OF PAIN ON EXCITATION OF THE HEART AND GREAT VESSELS

In work previously reported,[1] a method has been described for temporary occlusion of the coronary vessels in the unanesthetized dog, and also methods for the study of the production of pain and its transmission. This work was originally begun with the idea of studying the effects of temporary occlusion of the coronary vessels on the supposition that in this way we might simulate angina pectoris, if the theory that angina is produced by a temporary spasm of the coronary vessels is accepted.

As the work progressed, it became necessary to eliminate extraneous causes for pain,[2] which resulted in the study of pain sensation in the visceral and parietal pericardium, the myocardium and the great vessels, especially the first portion of the aorta. As a result, this investigation developed into three phases: (1) the physiologic effects of temporary occlusion of the coronary vessels in the unanesthetized and anesthetized dog; (2) the study of production of pain in the heart and blood vessels, and (3) the results that were found to follow distention of the aorta, the aortic ring and the peripheral vessels.

THE PHYSIOLOGIC EFFECTS OF TEMPORARY OCCLUSION OF THE CORONARY VESSELS IN UNANESTHETIZED DOGS

Under ether anesthesia, without the use of morphine or any other sedative, and with artificial respiration, the chest was opened in the fifth left intercostal space, exposing the parietal pericardium. Through a small incision in the parietal pericardium, a ligature was passed around the ramus descendens anterior sinister branch of the left coronary artery; without being tied, this ligature was passed through a flanged

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1. Sutton and King: Physiological Effects of Temporary Occlusion of the Coronary Vessels, Proc. Soc. Exper. Biol. & Med. **25**:842, 1928. Sutton, D. C.: Studies of the Mechanism of the Production of Cardiac Pain, Tr. Institute of Med., Chicago, February, 1929.

2. Pain is presumed to be present when a trained animal otherwise quiet becomes restless, moves and gives other evidence of distress during any procedure.

glass tube (fig. 1) which led the two ends to the surface; a purse string suture closed the pericardial incision and at the same time included the flange of the glass tube, thus fixing the tube in place. The proximal end of the tube was sutured in the wall of the chest, and the incision was closed, care being taken to remove any pneumothorax.

After three or four hours the animal had completely recovered from the anesthesia, was active, showed little shock from the operation and apparently suffered no pain. By fixing of the external portion of the glass tube and drawing lightly on the ligature, the artery and included tissue, which usually includes also the accompanying vein, were compressed.

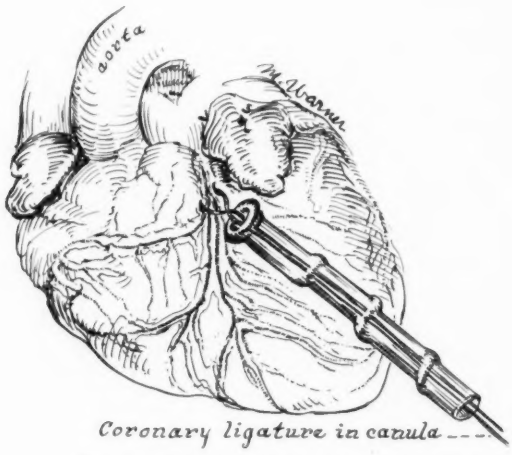

Fig. 1.—Coronary ligature and glass cannula.

This series of dogs was prepared as described, by passing a ligature around the ramus descendens anterior sinister, through a glass tube, and allowing the animal to recover completely from the anesthesia.

Dog 1.—The operation was performed as described. Three hours after operation the dog had completely recovered from the anesthesia, was active and showed no evidence of pain; it lay quietly while the dressings were removed and the tube was manipulated. Pulling on the tube with displacement of the pericardium produced no pain. Slight traction on the ligature caused uneasiness with stiffening of the legs, especially the left foreleg; moderate traction produced restlessness and whining, and strong traction sufficient to occlude completely the artery produced restlessness and other evidences of severe pain. During this period salivation was marked.

Numerous repetitions always gave the same results. The pain began immediately on beginning of traction and ceased promptly with its release. Finally, too strong traction was made so that the artery was torn in two. The pain promptly ceased.

Electrocardiographic tracings taken from lead II show a normal rate of 128 with an R wave 3.8 millivolts in height, and a T wave 0.6 millivolts in height. On the first traction an immediate paroxysmal attack of premature contractions of ventricular origin was seen, with a rate of 150. On second traction there were pauses of a second's duration, followed by rapid premature contractions of ventricular origin. The T wave was 1.4 millivolts. The third traction produced immediate paroxysms of premature contractions of ventricular origin, showing an average T wave 1.6 millivolts in height. The fourth traction resulted in complete cardiac standstill for five seconds. The fifth traction resulted in pauses of one second's duration. In no lead was there an inversion or change in the T wave other than that of increase in height.

After completion of the experiment, the chest was opened under general anesthesia; the pericardium was found to be distended and tense, so that on opening, the heart bulged through. All chambers of the heart were greatly distended. The location of the ligature was verified, the artery being torn in two, one-half inch distal to its origin.

Dog 2.—The operation was done as in the preceding experiment. Four hours after completion of the operation, the animal was in excellent condition, running about the room and giving no evidence of pain. It lay quietly until traction was made on the ligature, which produced moderate pain, restlessness and increased respiratory movements. The pulse increased in size and in rate at the beginning of the contractions, and there were frequent premature contractions. On prolonged traction, the pulse became more rapid and smaller. Pain ceased promptly with cessation of traction. Traction was repeated many times with the same results.

On opening the chest under anesthesia, all chambers of the heart were found to be dilated. The ligature was found to include the vein only. (Therefore occlusion of the coronary vein accompanying the ramus descendens anterior sinister produced pain.)

Dog 3.—The dog was operated on as in the preceding experiments. Five hours were allowed for recovery. The dog was in good condition, apparently suffering no pain. Traction produced immediate pain followed by rapid irregular pulse and salivation. During traction, along with the marked respiratory stimulation (fig. 2) there was a marked sinus arrhythmia. The pain ceased promptly on release of traction. After several temporary occlusions, 3 mg. of atropine sulphate was injected intravenously. The atropine greatly increased the pulse rate and caused complete disappearance of the sinus arrhythmia. Slight traction produced marked pain, which disappeared promptly on cessation of traction.

On opening the chest under general anesthesia, moderate dilatation of all chambers of the heart was found. The ligature was found to be around the artery and vein, three fourths of an inch distal to its origin.

Dog 4.—The animal was prepared as in the preceding cases and allowed four hours for recovery. The condition was good, with apparently no pain. Traction produced immediate pain with salivation, the pain ceasing when traction was released. Pain appeared to vary with the degree of traction. The animal vomited during traction.

The electrocardiogram shows a normal rate of 132, with an R wave in lead II of 1.5 millivolts, and a T wave of 0.5 millivolts. The wave was notched in lead II. First traction produced only an increase in rate; the second traction increased the rate to 168 per minute, with pauses of from one to one and one-half seconds' duration. The T wave was 0.7 millivolts and was not notched. The third traction produced a pause of one and one-half seconds' duration. The T wave was notched 0.4 millivolts. The fourth traction produced a rate of 168. The T wave

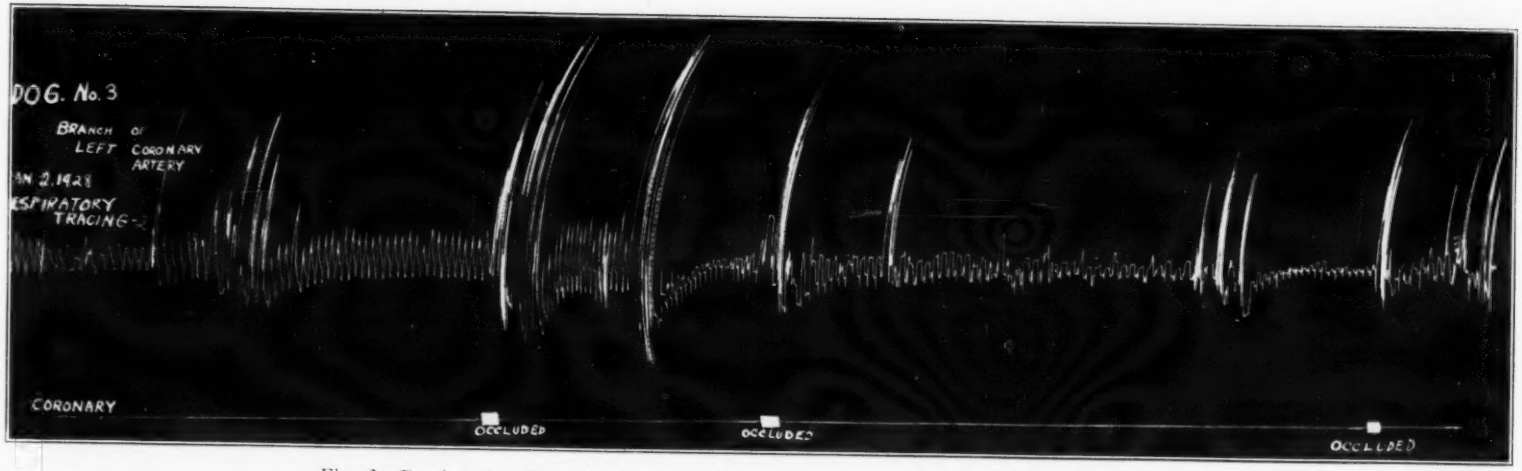

Fig. 2.—Respiratory effect of temporary occlusion of ramus descendens anterior sinister in dog 3.

was notched at times, almost iso-electric. The R wave was 4.8 millivolts. The fifth traction T wave was 1.2 millivolts and was notched. The P wave arose from the down strokes of the T.

Opening of the chest under ether anesthesia revealed moderate dilatation of all chambers of the heart, the ligature surrounding the artery one-half inch distal to its origin.

Dog 6.—The animal was prepared as in the preceding experiments, and about three hours were allowed for recovery. Slight traction produced pain and marked respiratory stimulation. Strong traction produced severe pain. The pain ceased immediately on cessation of traction.

The electrocardiogram showed a normal R wave of 1.6 millivolts, and a T wave of 0.3 millivolts. The rate was 168. The rate following the first traction was 168, with marked arrhythmia of the sinus, the T wave rising sharply from the down stroke of the R wave. The T wave was 0.4 millivolts; the P wave, 0.4 millivolts. On second traction, the R wave was 2.4 millivolts; the T wave, 1.6 millivolts, and the P wave, 1.2 millivolts. The rate was 144. Following the third traction, the R wave was 2 millivolts; the T wave, 2 millivolts, and the P wave, 1.4 millivolts. The T wave was notched on the ascending limb; the rate was 144. This dog was allowed to live two days. On the second day, traction produced pain. The location of the ligature was verified at autopsy, one-fourth inch distal to the origin of the artery, the animal having died of pericarditis.

Dog 8.—The dog was prepared as those in the preceding experiments, with the exception that the ligature was passed around a small branch of the ramus descendens anterior sinister. A second ligature was passed so as to include only muscle and pericardium, this ligature being passed through the same tube. Recovery was good. Traction of the ligature on the artery produced moderate pain, giving the impression that the severity of the pain may be in relation to the size of the artery occluded. The suture placed only in the muscle produced no pain on traction. Traction on each ligature was repeated many times with a constant repetition of the result. Finally the ligature in the myocardium tore through the muscle and pericardium without producing pain.

Autopsy verified the location of the first ligature around a small branch, and also showed that no vessel of macroscopic size was included in the second ligature. There was no increase in the size of the cardiac cavities.

Dog 10.—The animal was prepared as in the preceding experiment (dog 8), with one ligature around the artery near its origin, another including the muscle only. There was marked salivation for a period of one hour during recovery. Traction on the artery produced pain repeatedly. Traction on the muscles produced no pain.

Dog 5.—The animal was prepared as dog 1, with the exception that both vagi were severed during the operation. The animal was allowed four hours for complete recovery, and was in good condition except for a moderate cyanosis due to a partial pneumothorax.

Traction produced pain immediately, which ceased on release of traction; salivation was marked. Repeated tractions gave the same result. Under general anesthesia the chest was opened, and the heart was found to be greatly dilated in all chambers; the ligature was found to be around the vein only, one-half inch from the ramus descends anterior sinister.

The anoxemia from the pneumothorax is believed to be a factor in the production of the great dilatation of the whole heart.

Dog 7 A.—On March 10, 1928, the annulus of Vieussens was removed under general anesthesia. The dog recovered without any complications. On March 24, the dog was prepared as those in the preceding experiments, and after four hours had completely recovered from the operation and showed no symptoms when either the wound or the tube was handled. Traction repeated many times invariably failed to produce pain. The dog was allowed to remain alive until March 27, during which time repeated attempts to produce pain by traction on the ligature resulted in failure. On opening the chest under general anesthesia the heart was found to be moderately dilated, local pericarditis was present at the point of the opening and the ligature was found to include the artery and vein one-half inch from the origin of the ramus descendens anterior sinister.

Dog 7 B.—On March 17, 1928, the annulus of Vieussens was removed, the dog making a complete recovery without infection. On March 31, the dog was prepared as in the preceding experiments, three and one-half hours being allowed for recovery. In this animal, repeated attempts to produce pain by traction on the ligature resulted in failure. Pulling on the tube so as to stretch the parietal pericardium and displace the heart produced no pain. Salivation at times was marked during stretching. Under general anesthesia the chest was opened; the heart was found to be moderately dilated and the ligature was around the artery and vein at the origin of the artery.

Dog 9 A.—On March 31, 1928, the annulus of Vieussens was removed, the wound healing without infection. Seven days later the chest was opened as in the preceding experiments, and the ligature was passed around the artery. On repeated traction, no pain was produced. The chest was opened under general anesthesia, and the heart was found to be moderately dilated. The ligature was about one-half inch from the origin of the artery.

Comment on Results of Temporary Occlusion.—As previously stated, after the animal has recovered from the effects of the anesthesia, it is in surprisingly good condition. In the opening of the chest, muscles are displaced without being cut or torn, so that on recovery respiration and use of the limbs seem to cause no pain. Manipulation of the slightly protruding glass tube produces no pain.

Pulling the tube through the wall of the chest so that the parietal pericardium is stretched produces no pain. Pulling until the heart is displaced produces no pain.

The effects of compression of the artery are:

1. The moment the lumen of the artery is narrowed there is distinct evidence of pain, shown by restlessness of the animal. This pain ceases immediately on the return of the artery to its normal size.

2. Increasing narrowing of the arterial lumen produces increasingly severe pain, until total occlusion produces apparently severe pain. This disappears immediately on the release of occlusion.

3. As shown in dog 8, apparently the pain varies not only with the degree of obstruction but also with the size of the vessel occluded, being increased in severity by increase in the size of the artery.

4. Pain has been pronounced in every experiment, but there is some variation in the degree of pain in various animals. This variation may be due to one of two causes: first, some animals are less sensitive to pain than others; second, in some dogs' hearts there is a large anastomosing artery between the anterior descending and the circumflex arteries. This anastomosis occurs distal to the point of the ligature, usually through the first branch, to the left toward the apex, of the ramus descendens anterior sinister. This anastomosis is sufficiently large to prevent at times the formation of an infarct when the artery is tied proximal to it.

5. In two experiments, dogs 2 and 5, the vein only was included in the ligature. In these instances the pain was of the same character as in the other experiments, and the fact that the vein only was included in the ligature was not suspected until it was observed at autopsy.

6. The pain produced by compression of the artery and vein is not produced by compression of the muscle and visceral pericardium included in the ligature. This is definitely shown by the failure to produce pain by ligatures passed so as to compress only muscle and visceral pericardium. Even the tearing of the muscle and visceral pericardium when the ligature is pulled until it cuts entirely through both fails to produce pain.

7. When the traction is sufficiently forceful to tear out the ligature, the pain ceases immediately. Explanation for this cessation of pain is offered subsequently.

8. Salivation, which is accepted as evidence of nausea in the dog, has been observed repeatedly during the periods of compression. Dog 4 vomited at the time of complete occlusion of the vessel.

9. Respiration becomes increased in rate and volume as the pain increases, finally becoming violent and irregular. A symptomatic dyspnea is the first evidence of compression and may be the only evidence of moderate occlusion.

10. Section of the vagi or their paralysis with atropine interferes in no way with the production of pain by occlusion of the artery. Respirations were of the type following vagal section, and were unaffected by occlusion of the coronary artery. After vagosection, salivation occurred during traction.

11. Removal of the annulus of Vieussens completely abolishes all pain produced by compression of the vessels, although salivation may occur. Respiration is unaffected.

After repeated temporary occlusion of the vessels, when the dog is killed for autopsy (which is done in every experiment), the heart is found to be increased in size in all its chambers ("acute dilatation"). The degree of dilatation varies in different animals. This variation may

be due to the anastomosis between the anterior descending and the circumflex artery.

It has also been observed in experiments not here recorded that anoxemia during the period of anesthesia or from pneumothorax greatly increases the degree of dilatation following partial or complete occlusion of the ramus descendens anterior sinister.

Electrocardiographic studies made on the dogs with intact extrinsic cardiac nerves during periods of temporary traction show first a pause, followed by premature contractions, usually of ventricular but occasionally of auricular origin. At the beginning of traction, complete cardiac standstill has occurred for periods of from one to five seconds. Short periods of paroxysmal tachycardia have occurred, and on one occasion temporary occlusion produced an auricular fibrillation. There is a marked increase in the amplitude of both the R and the T waves. Inversion of the T wave has been observed only once; but in all cases it arises before the end of the down stroke of the R, as occurs in electrocardiograms after coronary occlusion in human beings.

THE PHYSIOLOGIC EFFECTS OF TEMPORARY OCCLUSION OF THE CORONARY VESSELS IN THE ANESTHETIZED DOG

For direct observation of the heart, a second series of experiments was done in which light barbital anesthesia and artificial respiration were used. The chest was laid open and the parietal pericardium was incised, the entire heart being exposed. The heart was kept moist with warm physiologic solution of sodium chloride. Myocardiographic levers were attached to the apex of the right ventricle and the left auricular appendage, and led to tambours writing on a smoked drum. The blood pressure was recorded directly from the left carotid artery by means of a mercury manometer. A ligature was passed around the coronary artery and through a glass tube which was inserted through a stab wound of the wall of the chest, exactly the same procedure as used in the preceding experiments. This technic enabled the direct observation of the changes in size, color and rhythm of the heart, also the recording of the ventricle and auricle, with simultaneous blood pressure curve.

Dog 100.—With the dog under barbital ether anesthesia, the chest was opened. Myographic levers were attached to the apex of the right ventricle and the end of the left auricle. The blood pressure was taken from the left carotid. A ligature was passed around the ramus descendens, one-fourth inch below its origin, as previously described. Traction produced a decrease in amplitude followed by an increase; the rate was slowed, then increased and irregular. The ventricular rate was increased with marked variation in amplitude. The blood pressure fell at times from 30 to 50 mm. of mercury. Immediately at the beginning of traction the vein included in the ligature became distended, the apex became first cyanotic, then pale, with a rapid increase in both auricular and ventricular volume.

Both vagi were sectioned. As a result, traction failed to lower the blood pressure. Ventricular amplitude was increased, but the rate was the same throughout for the autricle. The apex of the left ventricle became cyanotic. Both auricle and ventricle were increased in volume during traction (fig. 3).

Dog 102.—The animal was prepared as was dog 100. Traction caused first a decrease and then an increase in auricular amplitude. The ventricle was less affected than in the preceding experiment. The blood pressure fell slowly but definitely. Respiration was increased in amplitude and rate, as shown by increased diaphragmatic movements recorded by pneumograph attached to the abdomen. The tip of the ventricle became cyanotic during traction, and both ventricle and auricle became increased in volume. Attempted ligation of the circumflex failed, due to laceration of the arterial wall with hemorrhage. Following this there was a great increase in blood pressure, and the heart dilated slowly.

At autopsy it was found that there were three coronary arteries: the anterior descending and the circumflex which consisted of two separate arteries with two orifices. The anterior descending was surrounded by the ligature.

Dog 103.—With the dog under barbital ether anesthesia, preparation was made as in the experiment with dog 100. The ligature was placed around the ramus descendens anterior sinister, three eighths of an inch below its origin. Tracings of the auricle and ventricle were poor because of mechanical difficulties. Traction caused decrease of amplitude of the auricle with later increase. The ventricle dilated with premature contractions. At the beginning of traction the rate was increased, followed by increase in amplitude. The blood pressure fell with each traction. The vagi were sectioned during traction. The cardiac rate was increased. Only a slight fall in blood pressure occurred and was maintained at the lower level. Before section of the vagi, respiration (recorded as in the preceding experiment) increased in rate and decreased in amplitude. This rate continued after the first traction and did not change until after the vagi were severed. The apex of the left ventricle became cyanotic, and dilatation promptly followed traction (fig. 4).

Dog 104.—With the animal under barbital ether anesthesia, it was prepared as was dog 100. The left ramus descendens anterior sinister was ligated one-fourth inch below the bifurcation. With a slight increase in auricular amplitude during the traction, the ventricle became cyanotic over the area supplied by the artery with only slight dilatation during traction. Premature contractions were produced at the beginning and end of traction, ventricular amplitude being increased throughout traction. The blood pressure showed a moderate fall with each temporary occlusion. Both vagi were sectioned during traction, which was followed only by a moderate fall in blood pressure. The animal was allowed to become anoxemic by shutting off the artificial respiration which resulted in marked increase of irritability of the heart muscle during traction and greatly increased fall in blood pressure. Four cubic centimeters of digitalis was injected intravenously which resulted in no change following traction further than increased muscular irritability. Respiration showed no change during traction (fig. 5).

Dog 105.—The dog was prepared as the others of this series, the ligature being passed around the left ramus descendens. Traction produced marked fall in blood pressure. The ventricular wall included in the distribution of the artery became markedly cyanotic, but no dilation of the ventricle occurred. Increased amplitude of both auricular and ventricular contractions during traction was noted. Respiratory movements were increased during traction. The annulus of Vieussens was removed. During traction the blood pressure fell. The left vagus was severed, following which there was only a slight fall of blood pressure on temporary occlu-

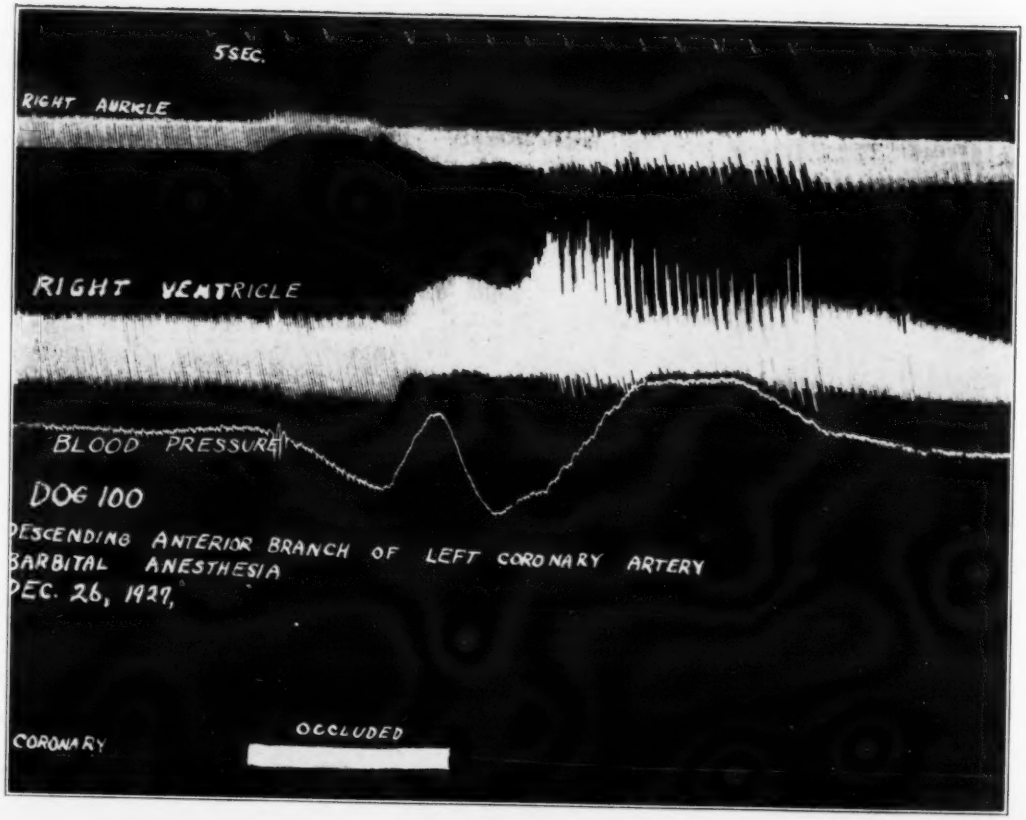
5SEC.
RIGHT AURICLE
RIGHT VENTRICLE
BLOOD PRESSURE
DOG 100
DESCENDING ANTERIOR BRANCH OF LEFT CORONARY ARTERY
BARBITAL ANESTHESIA
DEC. 26, 1927
CORONARY
OCCLUDED

Figure 3

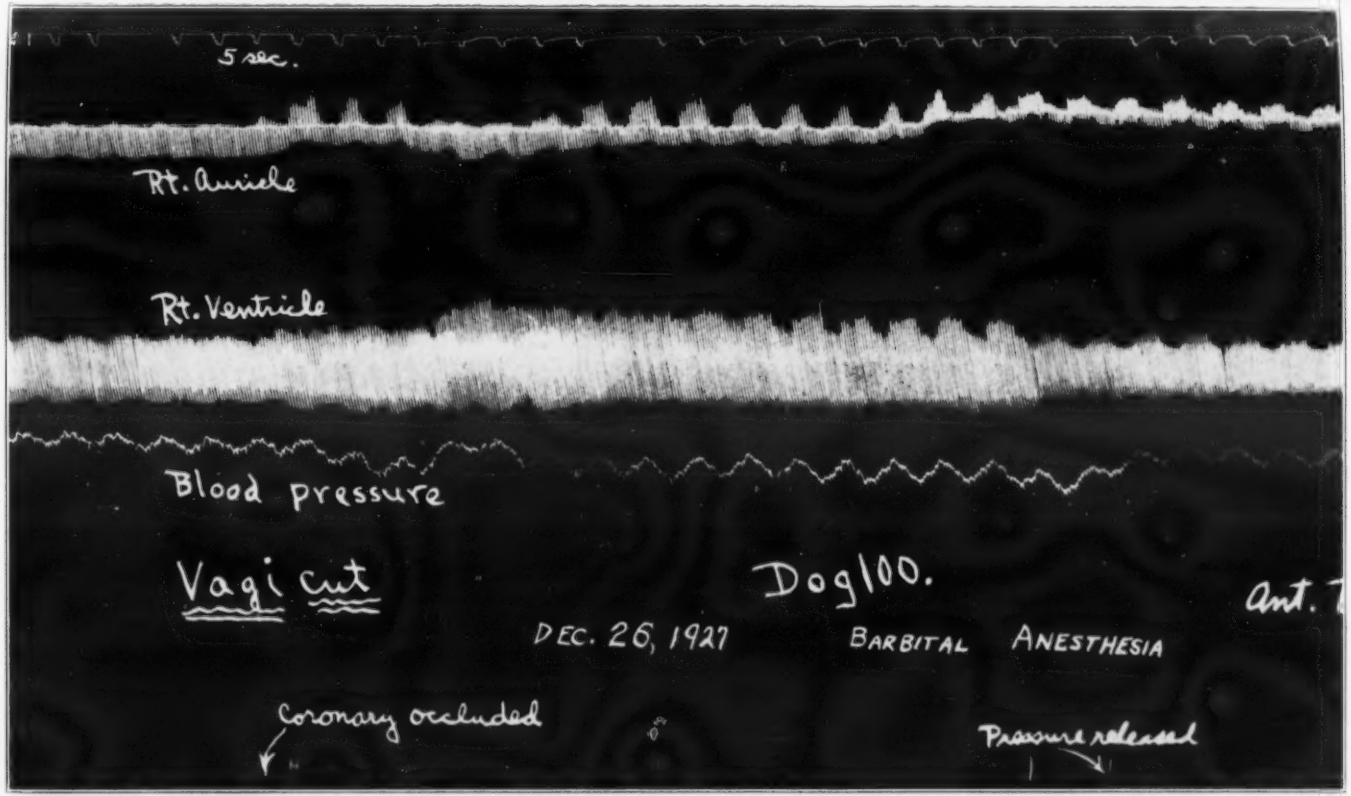

Figure 3

Fig. 3.—Curve for dog 100. There was a fall of blood pressure of 40 mm. of mercury. No fall occurred after section of the vagi.

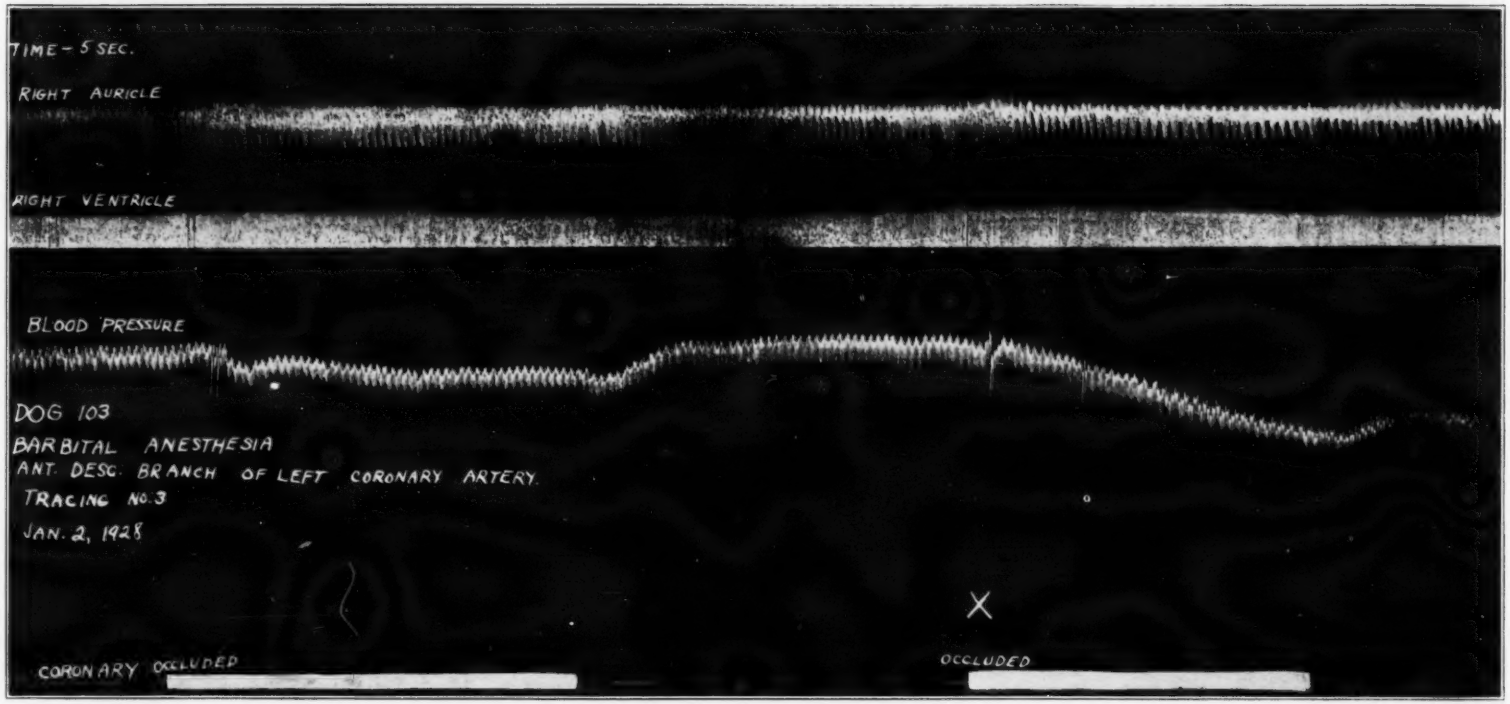

Fig 4.—Curve for dog 103. First gradual fall of blood pressure of 60 mm. of mercury. Note ventricular standstill at beginning of occlusion.

sion of the artery. The auricle and ventricle fibrillated for a short period spontaneously and then returned to normal rhythm.

Dog 106.—The animal was prepared in the same way as dog 105. The first traction produced a sharp fall in blood pressure of 48 mm. of mercury, with short ventricular standstill. Later tractions showed less change in blood pressure, but greater ventricular and auricular irritability.

Removal of the left stellate ganglion caused disappearance of the fall of blood pressure on traction, but the second traction produced greater irritability and increased amplitude of both auricular and ventricular tracings. After cutting of the left vagus this increased irritability and increased amplitude were not evident. Anoxemia caused lessened amplitude with increase in rate during traction, with greatly increased amplitude after release of traction. Final permanent occlusion produced auricular and ventricular fibrillation. Anoxemia greatly increased the dilatation of all cavities during traction.

SUMMARY AND CONCLUSIONS

Compression of the artery, vein and included tissue produces first a cyanosis of that portion of the ventricle supplied by the vessels; the vein becomes distended, while the myocardium becomes definitely paler. Almost immediately there is a definite and at times a marked increase in the volume of both ventricles and later also the auricles. Immediately following partial compression of the vessels there is a definite, rapid fall in blood pressure, amounting to from 30 to 50 mm. of mercury. Marked irregularities occur, as: (1) temporary ventricular standstill or cardiac standstill followed by many premature contractions, usually of ventricular origin, but also often of auricular origin; (2) paroxysmal tachycardia of both ventricular and auricular origin; (3) auricular fibrillation; (4) ventricular fibrillation; (5) "acute dilatation" of all the chambers of the heart; this is increased by anoxemia. With section of the vagi, compression does not result in any fall in blood pressure, except such fall as may occur as a result of ventricular or cardiac standstill.

Symptoms analogous to those occurring in man in angina pectoris and coronary occlusion can be produced experimentally in the dog; namely, pain, sometimes nausea and vomiting, stimulation of respiration and fall in blood pressure. Pain is abolished by removal of the annulus of Vieussens. It is suggested that sudden death in angina pectoris may be the result of ventricular fibrillation occurring during temporary decrease in coronary flow.

PRODUCTION OF PAIN BY EXCITATION OF THE PERICARDIUM, HEART AND GREAT VESSELS

As shown in the preceding paragraphs, temporary occlusion of a branch of the coronary artery alone or a coronary vein alone or of the two together invariably produces immediate, and in the larger vessels severe, pain. This pain disappears immediately on release of com-

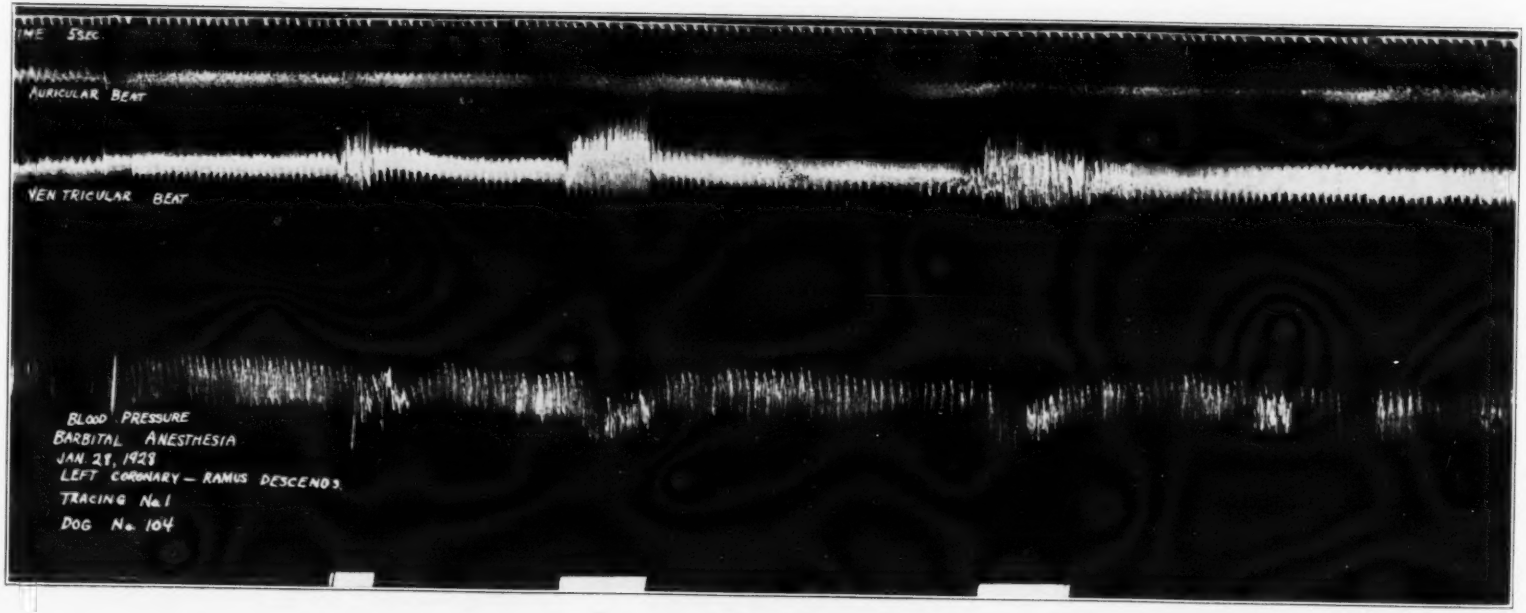
TIME 5SEC.
AURICULAR BEAT
VENTRICULAR BEAT
BLOOD PRESSURE
BARBITAL ANESTHESIA
JAN. 29, 1928
LEFT CORONARY — RAMUS DESCENDS.
TRACING No. 1
DOG No. 104

Figure 5

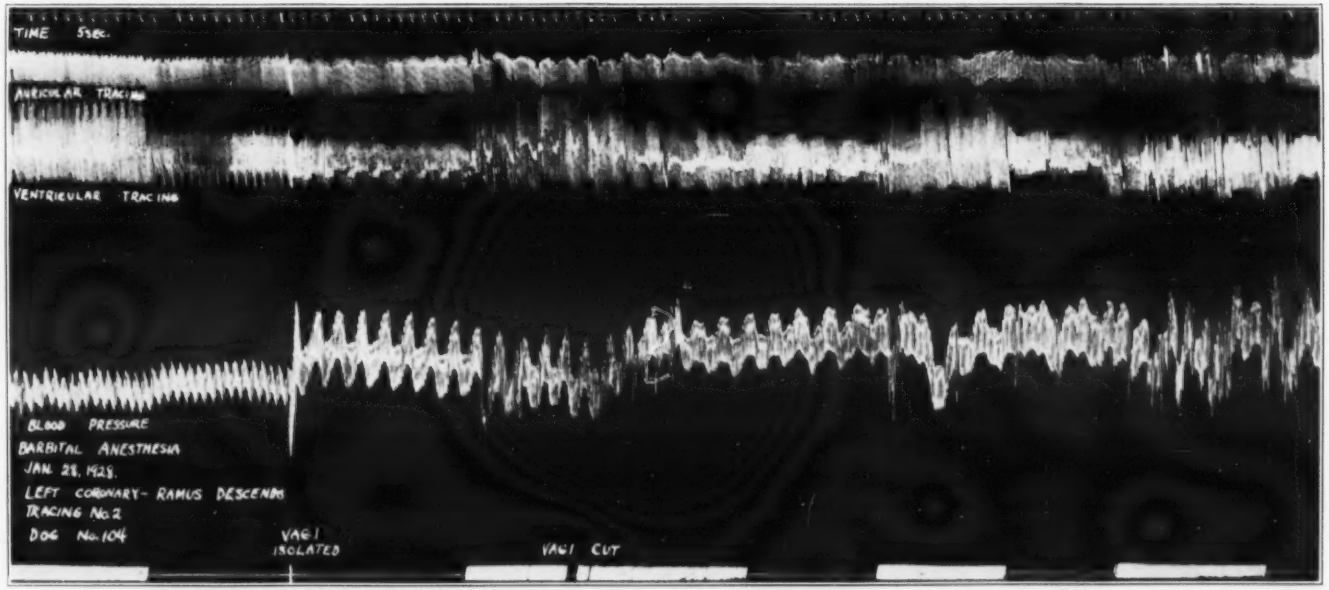

Figure 5

Fig. 5.—Curve of dog 104. In tracing no. 1, the changes in the ventricular rhythm and amplitude should be noted; in no. 2, the effect of section of the vagi is shown.

pression of the vessel. To exclude the possibility that this pain is produced by compression of nerve trunks that are closely associated with the vessels or their surrounding tissue, the ramus descendens anterior sinister is carefully dissected out over a short distance near its origin and painted with 80 per cent alcohol, which is not allowed to spread over the surrounding tissues. The ligature is passed around the artery, as described previously and passed through the tube; the pericardium and the wall of the chest are sutured, and the dog is allowed to recover from the anesthesia.

Dog 200.—With the dog under ether anesthesia, the ramus descendens anterior sinister was dissected out as already described, the wall of the artery was painted with alcohol and the animal was allowed to recover. Repeated traction with temporary occlusion of the artery failed to produce pain. The location of the ligature was verified by autopsy, and the heart was found to be moderately dilated.

Dog 201.—Under preparation as in the preceding experiment, the artery and vein accompanying were separately dissected out, individual ligatures being passed around each. The artery was painted with alcohol and the wall of the vein was left uninjured except for the trauma of dissection. Repeated traction on the artery failed to produce pain. Repeated traction on the vein produced moderate pain. The location of the ligature was verified by autopsy.

Dogs 202 and 203.—These animals were prepared as in the preceding experiments, the artery being dissected out and painted with 80 per cent alcohol. The animal was then allowed to recover. Repeated traction failed to produce pain. Dog 202 was markedly salivated during traction. In both dogs subpericardial injections of 10 per cent solution of ammonium hydroxide were introduced through a long needle passed into the glass tube. These injections failed to produce pain. The heart muscle was also perforated at a number of points with a coarse wire passed through the glass tube, without the production of pain.

Dogs 204, 205 and 206.—These animals were prepared as in the preceding experiments, the artery in all cases being painted with alcohol. Repeated traction on the ligatures failed to produce pain. These dogs were also given subpericardial injections of 80 per cent alcohol and 10 per cent ammonium hydroxide, without the production of pain. The mechanical perforation with a large needle also failed to produce pain. These procedures were carried out through the glass tube.

Dogs 207 and 208.—In these animals the artery was dissected out and the ligature applied as in the preceding experiment, but without the application of alcohol. On traction pain was produced as in all experiments of occlusion of the coronary. From 2 to 3 drops of alcohol were then applied to the denuded area of the artery by passing a long needle through a glass tube. After a few minutes, traction on the ligature no longer produced pain.

Dogs 209 and 210.—The ramus descendens anterior sinister was dissected out, the ligature passed around the artery and the animal allowed to recover. Traction in each of these dogs produced immediate pain, which disappeared on release of traction. Introducing a large needle through the glass tube, a drop of 80 per cent alcohol was applied to the artery at the point of ligature. Five minutes later traction failed to produce pain. One of these dogs was salivated during traction.

Summary.—From these experiments (dogs 200 to 210 inclusive) it appears that the pain fibers involved in experimental occlusion of the coronary artery are the nerve fibers that are found in the adventitia of the coronary artery or in the immediate surrounding tissues, and that the cutting of this pathway prevents the transmission of pain, which appears to be produced in the temporarily infarcted area of the heart muscle. This dissection of the fibers with the resultant cessation of pain explains the similar condition noted when the artery and vein were torn through by the ligature; namely, that the pain pathway is severed. The disappearance of pain after the tearing through of the artery and vein is also evidence against the fact that the pain may be produced in occlusion by the sudden distention of the artery proximal to the point of occlusion.

These experiments do not exclude entirely the possibility that pain is due to compression of the nerves. To eliminate that possibility, in two dogs the ramus descendens anterior sinister was injected with mercury at a point near its origin. In one, the mercury lodged at the first branch and was included in a firm thrombus. In the second, no mercury was found, but the artery as a result of injury was also filled with a firm thrombus. In both, an anemic infarct was found. On recovery, no objective evidence of pain was shown by either dog. Both were exercised by running until greatly fatigued, without the production of pain. This may be explained either on the ground that pain does not persist during the period required for the dog to recover from the anesthesia, which would be comparable to the cessation of pain in coronary thrombus in man, or more likely by the fact that dogs do not show evidence of continuous pain, unless extremely severe, in any manner like that resulting from a sudden pain.

The results of these two experiments did not assist in answering the question at hand; so no further experiments were performed.

Dog 300.—The chest of this dog was opened, and an incision was made through the parietal pericardium. An angulated needle was introduced into the ramus descendens, one-fourth inch from its origin, the point being passed toward the periphery. Three cubic centimeters of mercury was injected, the pericardium was sutured and the animal was allowed to recover as in preceding operations.

This dog was excited postoperatively, and was greatly salivated during the period of recovery. After recovery the animal apparently suffered no inconvenience. He was run approximately four blocks, at the end of which he collapsed with a rapid imperceptible pulse, but apparently suffered no pain. One hour later, he could not be tired by running.

With the animal under general anesthesia, the chest was opened, the right ventricle being found apparently contracted to a smaller size than normal. There was an area of definite anemia in the area supplied by the artery beyond the first branch after its origin. A drop of mercury was found at this branch firmly embedded in a thrombus.

Dog 301.—The animal was prepared as was dog 300. Mercury was injected into the artery one-fourth inch from its origin. Recovery was uneventful, apparently without pain. Four hours after anesthesia the animal was able to run indefinitely with apparently no inconvenience. At autopsy no mercury was found in any of the vessels, but there was a firm thrombus at the point of injection, and the area supplied by the artery showed a definite anemic infarct.

These experiments demonstrate that continuous occlusion of the coronary by a thrombus in the dog failed to cause objective evidence of continuous distress. Judging from the preceding experiments, these animals must have been distressed for a short period after the occlusion, which was not evident because of the anesthesia. These experiments, however, did not assist in answering the question of whether the pain on occlusion by compression was due to the obstruction per se or to the compression of nerves.

So, in a series of several dogs, in six of which success was obtained, one or the other coronary artery was blocked at its origin by the passing of a wire with a small knob on its end down the left carotid artery through the aorta and into either the left or the right coronary opening. Various wires have been used, the most satisfactory being a brass rod slightly smaller than the carotid. The end that is passed into the carotid is bent slightly, three eighths of an inch from the tip. Porter,[3] with the subject under ether anesthesia, introduced a glass rod [4] bent slightly at the top and introduced through an incision in the innominate artery. He said:

> The rod is passed down toward the left anterior sinus of Valsalva. As soon as the resistance of the aortic valve is felt, the rod is withdrawn a little and its head made to traverse the aortic wall near the bottom of the sinus. The opening of the left coronary artery will presently be found. Into this the rod is passed and fastened in place by tying a ligature around the innominate artery, including the rod. . . . Closure of the artery was always promptly followed by arrest. Fibrillary contractions were present in every case but one. . . . It seems hardly possible that the gentle introduction of the glass rod into the artery could in any way injure the artery.

METHOD

By our method, with the subject under procaine hydrochloride anesthesia the left carotid is dissected out and separated from the vagus nerve. Through an incision in the arterial wall the rod is passed carefully until it impinges on one of the aortic cusps. This is recognized first by ascertaining the length of the rod that will reach the cusps, and second, by the resistance encountered and the forceful pulsations that

3. Porter, W. T.: Further Researches on the Closure of the Coronary Arteries, J. Exper. Med. **1**:46, 1896.

4. The first mention of Porter's method was made in the Zentralbl. f. Physiol., 1895, no. 16, p. 481.

are transmitted through the rod. The rod is then turned so that the bent point is passed toward either the right or the left coronary orifice. This is more easily accomplished for the left than for the right orifice, and requires considerable practice.

Dog 500.—The carotid artery was dissected out and freed from surrounding structures, under local anesthesia, and the brass rod introduced as described. This was the first experiment of this series.

During manipulation of the rod a point was found which produced pain. On removal of the rod from this point, the pain immediately disappeared. The point was found again and the wire held firmly in place. This was done with a fear that the movement of the animal would dislodge the rod. Instead, the briefest moment of pain, dyspnea and rapid irregular pulse was followed by instantaneous death. This spectacular result precluded minute observation of events leading to death.

Careful dissection while the rod was held in place revealed the tip of the rod completely occluding the left coronary artery.

Dog 501.—After several failures to find the coronary, the technic was developed to a point where by measurements and the "feel of the rod" the orifices could be found with a large percentage of success.

In this dog, on passing the wire into the artery, an obstruction was felt, which was judged to be the left coronary orifice. Preceded by a moment of struggle and pain, death occurred suddenly. The movements dislodged the point in the orifice. The momentary occlusion apparently produced a cardiac damage from which the animal could not recover, possibly a ventricular fibrillation. When the chest was opened the auricles and ventricles were fibrillating.

By direct observation, the rod held in the same manner readily entered the orifice of the left coronary artery.

Dog 502.—The animal was prepared as in the second preceding case (dog 500). In this animal repeated touching of two points presumed to be the right and left coronary orifices produced pain, dyspnea and rapid irregular pulse. Apparently neither orifice was occluded sufficiently to cause death.

Under ether anesthesia the heart was exposed and the rod repeatedly passed to both coronary orifices by the same manipulations as those causing pain.

Dog 503.—The animal was prepared in the same way as dog 500. The rod was passed to a point in the aorta which produced pain, dyspnea and a rapid irregular pulse. The rod passed easily for an inch and one-half further. This animal was immediately killed by injection of ether intravenously.

The rod, which was smaller than the usual one, was found to have passed into the left coronary artery and down to the circumflex branch to the point of the curve downward over the ventricle (fig. 6).

Dog 504.—The dog was prepared as dog 500. In this experiment the tip of the rod was wound with cotton to form a small ball for complete closure of the orifice of the coronary. During manipulation the animal suddenly died in the same manner as dog 500.

Immediate examination revealed a long thrombus which had gathered about the cotton. One-half inch of this thrombus extended into the left coronary artery, completely occluding it.

Dog 302.—The animal was prepared as dog 500. The blood pressure was taken by inserting a cannula into the right femoral artery (under local anesthesia)

and connecting it with a recording mercury manometer. When the rod was passed down into the ascending aorta and turned so as to pass into the left coronary orifice, evidence of pain was produced with violent respiration, marked elevation and variation in blood pressure, followed by a rapid fall and death of the animal.

Examination of the heart and aorta showed the rod occluding the left coronary artery (fig. 7).

One of us (D. C. S.) once stood at the bedside of a young man who suddenly clutched his chest and with a look of anguish died. Autopsy revealed a large embolus completely occluding the orifice of the left coronary artery.

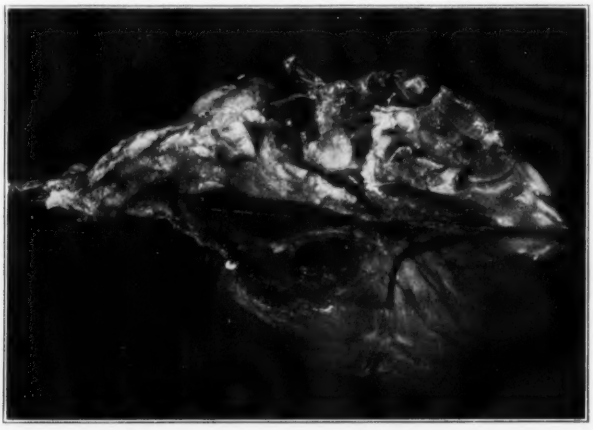

Fig. 6.—Rod inserted through the carotid and aorta into the left coronary artery and down the circumflex until it bulges out the pericardium.

Experiments on dogs 501 and 502, concerning which there might be some doubt because the coronary orifice was not found occluded at autopsy, undoubtedly were examples of true occlusions.

Repeated failures in which the aorta and heart were injured or perforated never showed the symptoms observed in coronary occlusion.

In the experiments in which a ligature was passed around the coronary artery and vein, on one occasion both were missed, and it was found that traction on the ligature did not produce pain. This was followed by passing the ligature through various portions of the anterior surface of the heart without the inclusion of vessels, with the result that traction or even tearing out of these ligatures in the conscious dog produced no pain. This apparent absence of pain from

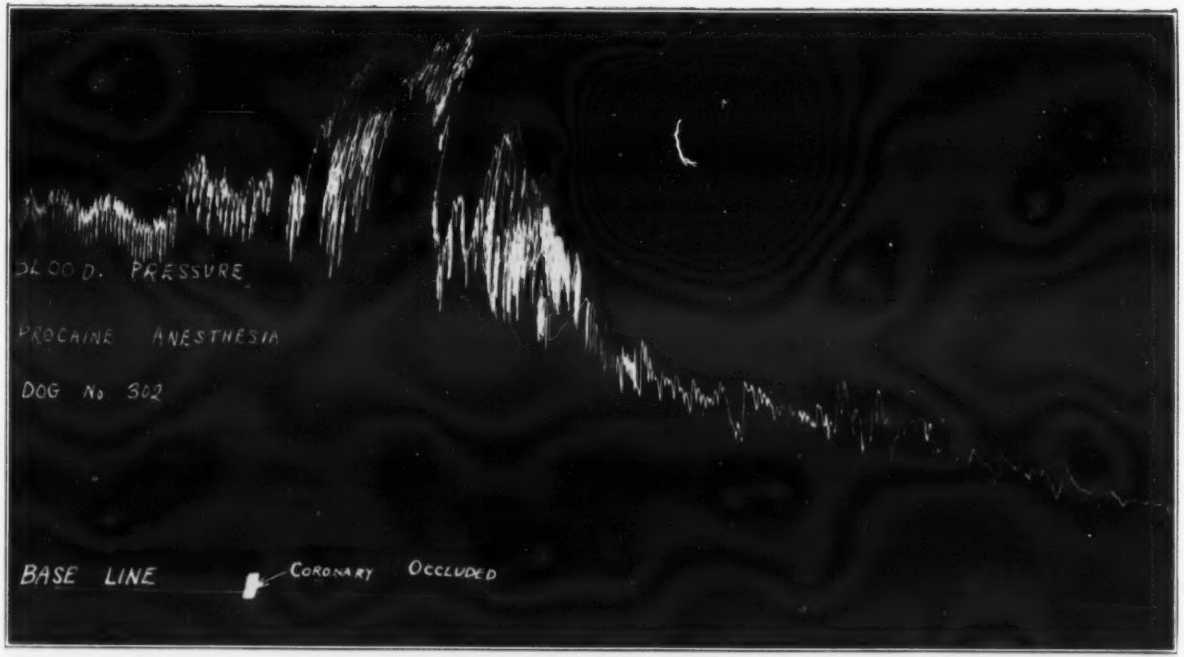

Fig. 7.—Blood pressure tracing in dog 302 taken at the time of occlusion of the coronary artery through the carotid artery, showing the effects of sudden complete occlusion of the left coronary artery on respiration and blood pressure.

mechanical stimulation of the myocardium and visceral pericardium was checked by further observations.[5]

These experiments were done either through a glass tube sutured into the pericardium as in preceding experiments or by injecting local anesthesia into the wall of the chest of the dog over the third, fourth or fifth interspace, a needle being passed directly through the chest and into the myocardium. The location of the puncture made in the myocardium was invariably checked by postmortem examination (fig. 8).

In dogs 204, 205 and 206 (the preceding protocols) the muscle and visceral pericardium was pierced at a number of points with a large hypodermic needle or a blunt wire through the glass tube already fixed in place. In four dogs a large hypodermic needle was introduced through the intact thoracic wall (local anesthesia having been induced in the skin and subcutaneous tissues). No pain was noted after the pleura was passed. Just as the heart was touched near the apex, occasional pain had been noted. This is interpreted as occurring at the moment of piercing the parietal pericardium.

In eleven dogs in which passing of the rod into the orifice of the coronary artery through the aorta was attempted, or in the use of the aortic dilator, accidental puncture of the heart muscle occurred. In

5. Willis, R.: The Works of William Harvey, printed for the Sydenham Society, London, 1847, p. 383. It is of interest to note that Harvey probably was the first to discuss sensation in the heart. A young nobleman, following a fracture of the ribs, had a large abscess which opened, leaving a large gaping wound on the left side. Charles I asked Harvey to see him and report on the case.

Harvey found an extensive ulcer, "into which I could readily place three fingers and a thumb. Which done, I straightway perceived a certain protuberant fleshy part, affected with an alternating extrusive and intrusive movement. This part I touched gently. Amazed with the novelty of such a state, I examined everything again and again, and when I had satisfied myself, I saw that it was a case of old and extensive ulcer, beyond the reach of art, but brought by a miracle to a kind of cure, the interior being invested with a membrane, and the edges protected with a tough skin. But the fleshy part (which I at first took for a mass of granulations), and others had always regarded as a portion of the lungs, from its pulsation motions and the rhythm they observed with the pulse—when the fingers of one of my hands were applied to it, and those of the other at the wrist—as well as from their discordance with the respiratory movements, I saw no portion of the lung that I was handling, but the apex of the heart covered over with a layer of fungous flesh by way of external defense, as commonly happens in old foul ulcers.

"Instead of a verbal answer, therefore, I carried the young man himself to the king, that His Majesty might with his own eyes behold this wonderful case; that, in a man alive and well, he might, without detriment to the individual, observe the movement of the heart, and, with his proper hand even touch the ventricles as they contracted. And His Most Excellent Majesty, as well as myself, acknowledged that the heart was without the sense of touch; for the youth never knew when we touched his heart, except by the sight or the sensation he had through the external integument." This is truly a royal experiment.

this manner, the muscle and visceral pericardium have been torn at the following points: (1) through the apex of the left ventricle; (2) through the aorta at the aortic cusp and on through the left auricle; (3) through the interventricular septum and out through the anterior or lateral wall of the right ventricle; (4) in one instance, through the aorta and then through the left auricle.

In no instance was definite pain noted. Hemorrhage into the pericardial cavity produced, however, marked restlessness and dyspnea.

In dogs 204, 205 and 206, 80 per cent alcohol was injected subpericardially without pain. The points of these injections were on both

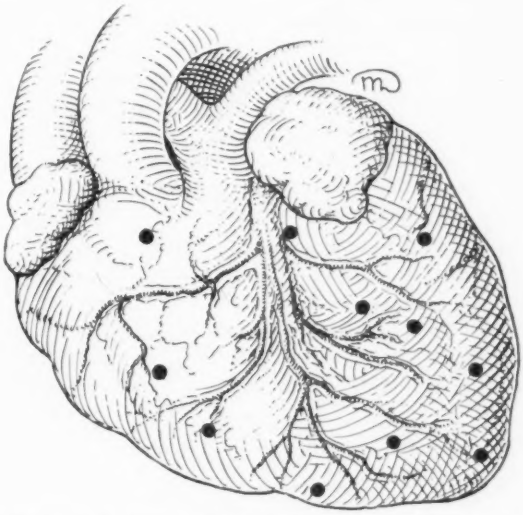

Fig. 8.—Diagram of heart; the black areas show points of mechanical and chemical stimulation of the visceral pericardium and myocardium.

sides of the ramus descendens anterior sinister. In no instance was pain produced.

Ammonium hydroxide, 5 and 10 per cent, was injected subpericardially into dogs 202 and 203, in about the same location as the alcohol. No pain was noted.

Into three dogs barium chloride (1 per cent and 5 per cent solutions) was injected through the cocainized wall of the chest into the apex and anterior aspect of the left ventricle. At postmortem examination in each instance an area of ischemia and localized retraction was found, the largest being 1 cm. in diameter. No pain was observed in this group.

In two dogs, 0.5 cc. of fluid extract ergotamine was injected through local anesthesia of the wall of the chest into the apex of the left ventricle. This produced no pain.

In three dogs, through local anesthesia of the skin, epinephrine, 1 : 1,000, was injected subpericardially, near the apex.

Dog A received an intramyocardial injection of 0.5 cc. of epinephrine near the apex, within a moment stood still, semirigid as if in pain, the left foreleg limped distinctly when forced to walk (the thoracic puncture of the preceding dogs did not produce this limp), soon vomited, and within ten minutes was apparently well. Two more injections of 0.5 cc. producted all the preceding symptoms except the limp on walking.

Dog B was given two injections into the myocardium of 0.5 cc. of 1 : 1,000 epinephrine, which resulted in a semirigid position following the injection, vomiting, but no disturbance of gait.

Into dog C, 1 cc. of 1 : 1,000 epinephrine was introduced through a locally anesthetized area of the thorax. This was injected in small amounts through several punctures into the myocardium. This animal suffered definite pain, limped with the left foreleg and vomited. Within ten minutes the animal was anesthetized and the heart was removed. An area 2.5 cm. in diameter of localized ischemia was found.

The interpretation of this experiment is modified by the fact that the injection of epinephrine into the heart muscle is absorbed almost as rapidly as an intravenous injection. The semirigid position of standing and the vomiting are probably due to the general effect of the epinephrine.

The limp of the left leg on two occasions can be interpreted only as referred pain from the myocardium. The pain shown by dog C is comparable to that of the closure of a small branch of the coronary artery.

In two dogs, injection of from 3 to 4 cc. of normal physiologic sodium chloride (with the idea of stretching the visceral pericardium) failed to elicit pain.

The pulling on the glass tube which was sewed into the pericardium of the dog resulted in no pain due to displacement of the heart or stretching of the pericardium.

In one monkey (*Macacus phenur*) the ribs and sternum lying immediately anterior to the heart were dissected away under local anesthesia, and the pericardium was incised, the heart being held toward the anterior wall of the chest by two fine forceps applied to the parietal pericardium. There was apparently no pain noted as a result of traction on the parietal pericardium. It was noted that when the forceps were clamped to the parietal pericardium, evidence of pain was elicited. Using a fine pair of forceps, pinching of the visceral pericardium of the anterior surface of the heart resulted in no evidence of pain. The heart was too small to pass the usual ligature. With a fine forceps, pinching of the circumflex branch of the coronary artery produced the same pain as in other methods of temporary occlusion. When the

tissues superficial to the artery were pinched without blocking the artery, no pain was produced. (Only one monkey was used as a check, as the results were entirely comparable with those found in dogs.)

SUMMARY AND CONCLUSIONS

It has been definitely shown that temporary partial or complete interference with blood flow in a coronary artery or vein invariably produces pain. This pain is apparently referred to the foreleg, as shown by: (*a*) rigidity of the left foreleg when the ramus descendens anterior sinister is ligated or temporarily occluded; (*b*) limping of the left foreleg after repeated temporary occlusions of the ramus descendens anterior sinister, and (*c*) limping of the left foreleg in two animals after intramyocardial injection of 0.5 and 1 cc. of 1:1,000 epinephrine. It is certain that this limp is different from that which occurs as the result of injury to the wall of the chest from the operation.

The nerve fibers responsible for conducting the pain sensations from the heart are those fibers in the adventitia of the blood vessels or adjacent tissues. This is indicated by the absence of pain after painting the stripped arterial wall with 80 per cent alcohol.

The tearing of the artery or veins also severs the nerve pathway, resulting in disappearance of the pain.

The pain is not produced by sudden distention of the arterial wall proximal to the point of occlusion, as closure of the orifice in the aorta produces pain without distention. Occlusion of the orifice also eliminates pressure on the nerves included in the ligature as a cause of pain.

The pain pathway to the brain is by way of the sympathetic, as shown by the presence of pain when the vagi are severed, and its abolition by removal of the stellate ganglion or the annulus of Vieussens.

Nausea, as evidenced by salivation in the dog, and actual vomiting have occurred as a result of temporary occlusion of the coronary artery. This occurred in two instances when the sympathetic pathway was interrupted, and possibly verifies the observations of Thatcher, that vomiting may occur reflexly from the heart.

Although the microscopic anatomy of the visceral pericardium shows a marked network of nerve plexuses which have been interpreted as sensory nerves, our experiments have failed to show any evidence of sensory nerves.

As shown by traction on the glass tube fixed to the parietal pericardium of dogs, (*a*) stretching of the parietal pericardium does not produce pain; (*b*) displacement of the heart does not produce pain, and (*c*) displacement of the aorta does not produce pain until the surrounding structures are disturbed.

On the other hand, evidence is shown directly in the monkey that mechanical stimulation of the parietal pericardium produces pain. Capps [6] has made similar observations in man.

From the evidence presented, the only cause of pain in the myocardium and visceral pericardium is the result of interference with the blood supply. This is in accord with the original theories of angina pectoris as expressed by Hunter, Jenner, Parry and others. The original theory presumes that interference to blood supply results from narrowing of the arterial lumen as in arteriosclerosis. Later the theory of vascular spasm (Blackhall, See, Huchard) was advanced to explain those cases in which no anatomic vascular changes are found, which results in the same interference with nutrition of the heart muscle.

Our experiments indicate that angina pectoris (or cardiac pain) is the result of insufficient nutrition to the heart muscle. This being true, it is readily conceivable that the anatomically normal heart may, under conditions of extreme exertion, fail to receive sufficient blood (nutrition) through normal coronary arteries. In fact, this is suggested in the sensations of athletes just before getting their "second wind." These sensations are choking sensations, substernal oppression or actual precordial or substernal pain.

Untrained subjects may experience sensations so severe as to prevent continuance of the efforts until the "second wind" comes. If intelligent patients suffering from angina pectoris are carefully questioned, a surprising similarity between the sensations of an extreme effort in youth and their present sensations during an attack of angina pectoris of effort is found. This similarity was first called to my attention (D. C. S.) by the unsolicited observation of a patient that the sensation felt as a young man after running up a mountain side, during an emergency, was exactly the same as that now felt during an attack of angina pectoris.

Wenckebach [7] drew similar conclusions in discussion of the "Töten Punkte" ("second wind") and angina pectoris. He further called attention to the fact that both are relieved by the administration of nitrites.

However, in hearts in which the blood flow is decreased by sclerotic narrowing of the lumen of the coronary arteries, much less exertion may result in sufficient interference with the blood flow to cause pain. In some cases there are apparently no or insufficient changes in the coronary arteries of persons who have suffered from angina pectoris during life to account for the pain as an obstructive phenomenon. In these cases a spasm of the coronary arteries has been presumed to exist, although sclerosis of the smaller vessels has not been excluded.

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6. Capps, J.: Tr. A. Am. Physicians **42**:243, 1927.

7. Wenckebach: "Töter Punkt"—"Second Wind" and Angina Pectoris, Wien. klin. Wchnschr. **41**:1, 1928.

Without denying the possibility of the existence of such a condition as vascular spasm, its presence is not necessary to explain anginal pain. For example, in the cardiac sensations of "second wind," or on exertion in the patient with cardiac disease, the sensations may be due to a failure of the coronary arteries to dilate and so supply the heart with an extra supply of nourishment to care for the extra work it is called on to perform. On this principle, drugs act beneficially in such cases by causing adequate dilatation to meet the demand of the cardiac muscle for proper nourishment. Under normal physiologic conditions, the coronary arteries are able to respond adequately up to the point of extreme exertion, or "second wind," when other extra compensatory factors enter in; but in the patient with angina, the coronary dilator mechanism fails to operate, and dilator drugs become necessary.

On the other hand, a large percentage of persons with most marked sclerotic changes have never suffered from angina pectoris. Variations in the increasing anastomosis of the coronary arteries that results with increase in age, as shown by Gross,[8] may well be the deciding factor. These variations in anastomosis offer an explanation for the absence of pain in cases of advanced coronary sclerosis. This offers an explanation for the rarity of nonsyphilitic angina pectoris in clinics attended largely by laborers. As a result of life-long strenuous exercise, a much more free anastomosis of the coronary arteries and a more responsive dilator mechanism might be expected in laborers than in those of more sedentary habits.

Experimentally, temporary occlusion of the coronary arteries has caused temporary pain, whereas permanent complete occlusion does not lead to permanent objective manifestations of pain in dogs; the sudden decrease in blood supply apparently causes the pain. The pain has persisted as long as compression has been continued in conscious animals, but is not evident after the animal with a permanent obstruction of the coronary artery has recovered from the anesthesia. The duration of the pain of permanent occlusion is less than the period required for recovery from ether anesthesia, and greater than even a ten minute temporary occlusion. If a limp in the left foreleg is accepted as evidence of pain, the persistence of pain after recovery from anesthesia has been observed.

This is at variance with the clinical presence of pain in cases of coronary thrombosis in which the pain may last from hours to days, unless a slowly forming retrograde thrombus with closure of additional small branches causing gradual increase in the ischemic area is the cause of prolonged pain. This is in accordance with conditions observed anatomically in cases exhibiting pain of long duration ending in death.

8. Gross, L.: The Blood Supply to the Heart, New York, Paul B. Hoeber, Inc., 1921.

Anoxemia as the result of pulmonary lesions, as emphysema, results in a constant undernutrition of the heart muscle, making it more susceptible to the effects of decrease in blood supply. It is well known that irritability of nerve endings is increased by lack of oxygen, but that they are anesthetized by prolonged asphyxia.

PAIN IN THE AORTA AND EFFECTS OF MECHANICAL DILATATION OF THE AORTA

Vaquez, Allbutt and others have suggested the hypothesis that the pain of angina pectoris is produced by dilatation of either the first portion of the aorta or the aortic ring. This theory is attractive and has been widely accepted because of the frequency of attacks of angina and spasmodic dyspnea in syphilitic aortitis and the aortitis following influenza.

We thought that it might be possible to test the theory experimentally. Accordingly, through the designing of an instrument that is best described by illustration (fig. 9), it is possible to stretch the aorta and aortic ring and other vessels, only local anesthesia being used for

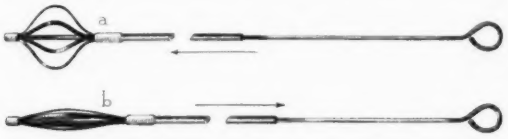

Fig. 9.—Aortic dilator (*a*) distended and (*b*) closed.

the insertion of the instrument into the artery. As in the experiments in which a rod is passed into the coronary orifices, the left carotid is dissected out under local anesthesia and freed from the surrounding tissue, especially the vagus nerve, with the minimum of injury.

UNANESTHETIZED DOGS

In a group of nine dogs under local anesthesia the left carotid artery was exposed and isolated and incised to introduce the aortic dilator. It is noted in all dogs that although there is some stretching of the carotid artery as a result of the size of the dilator, there is no objective evidence of pain as the result of forcing it through. The junction of the carotid and aorta at times offers resistance to the passage of the dilator. In no instance was pain observed as a result of passing this obstruction. The ascending portion of the aorta is located by passing the instrument onward until the tip impinges on the aortic valves. It is drawn from one-fourth to one-half inch away from the valves, so as to avoid stretching the aortic ring. At this point, the dilator is extended fully.

In no instance did stretching of the aorta produce any evidence of pain, although at postmortem examination the intima was found to be torn and lacerated as a result of the tension of the springs. Passing the dilator through the aortic ring, which is estimated by the distance the tube passes after impinging on the valves and dilating the

Fig. 10.—Tracing showing respiration in dog 30 with dilation of arch of aorta.

ring, fails to produce pain. Passing the instrument on into the ventricle, extending the dilator in the ventricle, produces no evidence of pain.

Stretching of the ascending aorta, aortic ring and cavity of the left ventricle always produces a marked spasmodic dyspnea. This ceases on release of the stretching (fig. 10).

When the tip of the dilator impinges on the aortic cusp, considerable pressure can be used before the cusp is perforated. The longitudinal

stretching of the aorta as a result of pressure on a cusp of the valve causes no pain. A spasmodic dyspnea is produced by longitudinal stretching.

Perforation of an aortic valve cusp produces no pain. The spasmodic dyspnea ceases as soon as the stretching of the aorta is relieved by the tearing of the cusp.

In the experiments on occlusion of the coronary artery through the aorta, the rod was pressed firmly against the aortic wall, mechanically irritating and tearing the intima, without production of pain. Also, in the attempts to occlude the orifice of the coronary and in the present experiment, the aorta was perforated either by too great pressure or by the breaking of the springs of the dilator.

As the result of these accidents, the following points have been perforated: (1) the carotid, at the junction of the aorta; (2) the arch opposite to the origin of the carotid; (3) the ascending aorta, and (4) the aortic ring. No immediate pain is noted as a result of perforation of the aorta. Later hemorrhage into the surrounding tissues produces spasmodic dyspnea and pain.

ANESTHETIZED DOGS

For the purpose of studying the effect on blood pressure, a group of dogs was prepared as in the preceding experiment, general instead of local anesthesia being used. Blood pressure was recorded by a cannula in either the right carotid artery or one of the femoral arteries.

Dog 601.—With the dog under morphine and light ether anesthesia, the left carotid artery was exposed and freed from surrounding structures. Through an incision of half the circumference, the instrument for stretching was inserted into the arch and ascending aorta. The left femoral artery was also exposed, and a similar instrument was introduced into the abdominal aorta. Blood pressure was recorded by cannula in the right carotid artery. Repeated dilatation of the ascending aorta and arch failed to produce any material change in blood pressure. The passing of a dilator into the aortic ring produced a marked fall of blood pressure (64 mm. of mercury) immediately on dilation, which returned promptly to normal on removal of pressure. This was repeated a number of times. Dilation of the abdominal aorta repeatedly showed no effect on blood pressure, but following release of the last pressure there occurred a delayed rise in pressure of 44 mm. of mercury, which was maintained throughout the remainder of the experiment (fig. 11). Both vagi were severed, following which dilation of the ascending portion and arch produced no fall in blood pressure, but dilation of the ring produced a fall (48 mm. of mercury).

Before section of the vagi in this animal, the annulus of Vieussens was exposed and its connections with the vagus severed. During manipulation it was found that the blood pressure rose sharply, to fall with the cessation of mechanical stimulation. Repeated stimulation of the severed annulus of Vieussens and stimulation mechanically and electrically of the various branches to the cervical sympathetic produced a prompt definite rise in blood pressure (16 to 32 mm. of mercury) (fig. 12).

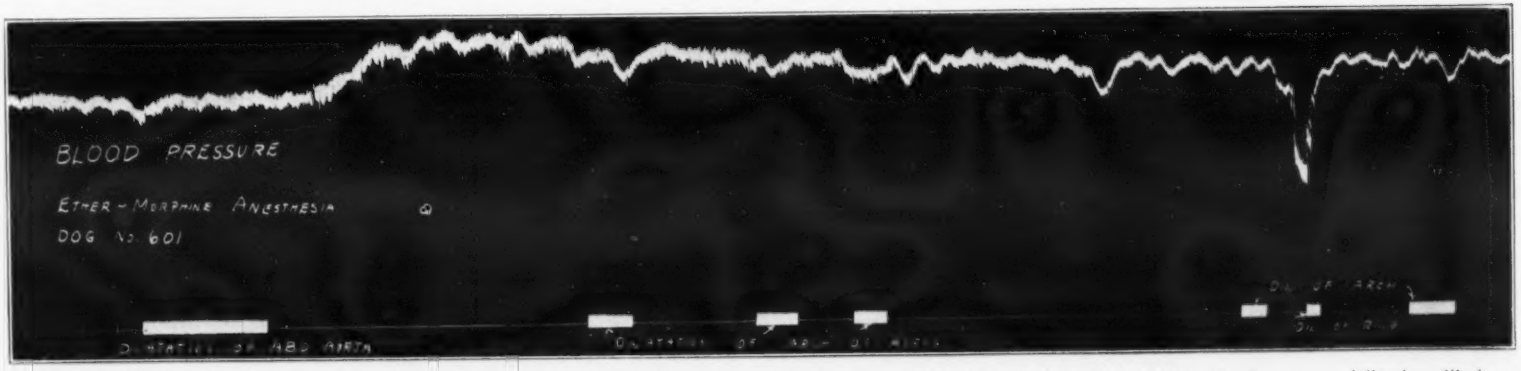

Fig. 11.—Curve for dog 601. Note lack of response during dilation of the abdominal aorta with delayed rise; slight fall in blood pressure following dilation of the arch of the aorta, and marked fall in blood pressure (66 mm. of mercury) during dilation of the aortic ring.

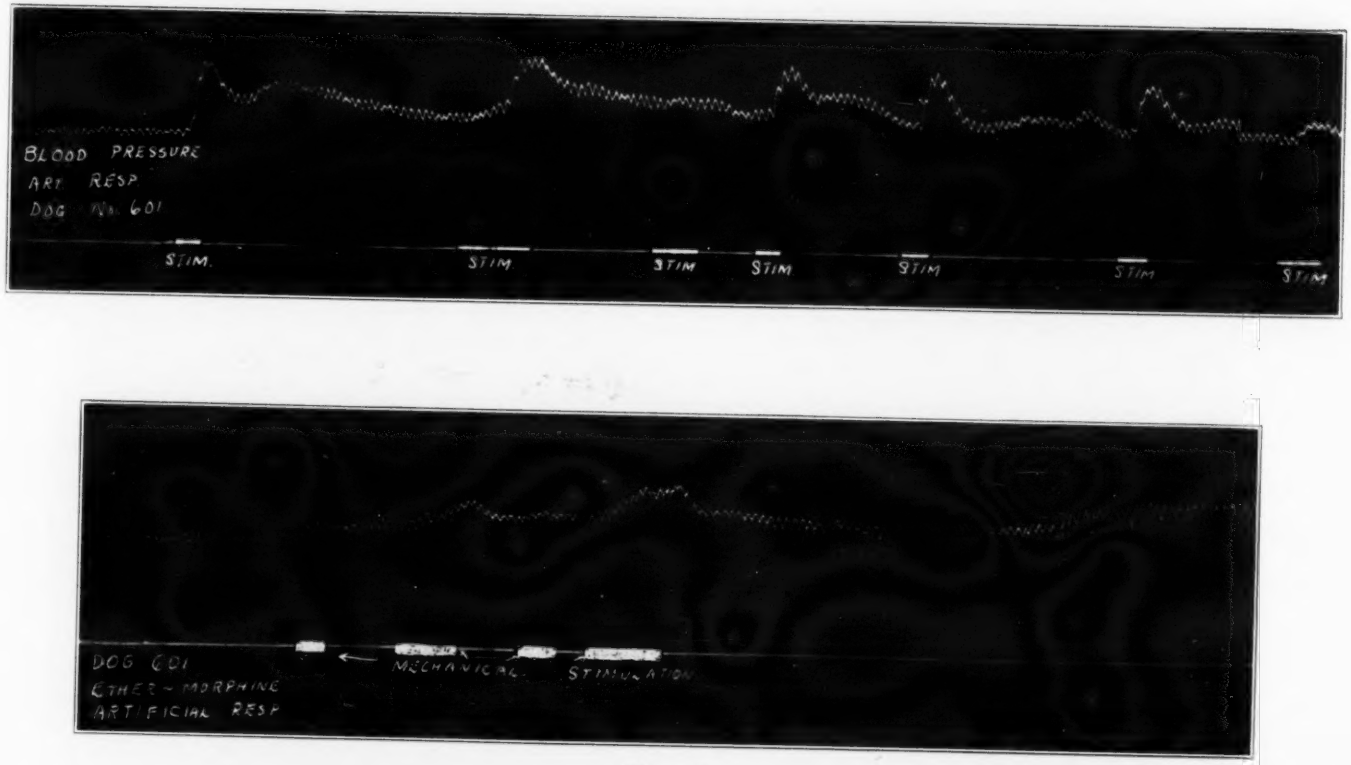

Figure 12

Fig. 12.—Curve for dog 601, showing the effect of electrical and mechanical stimulation of the annulus of Vieussens.

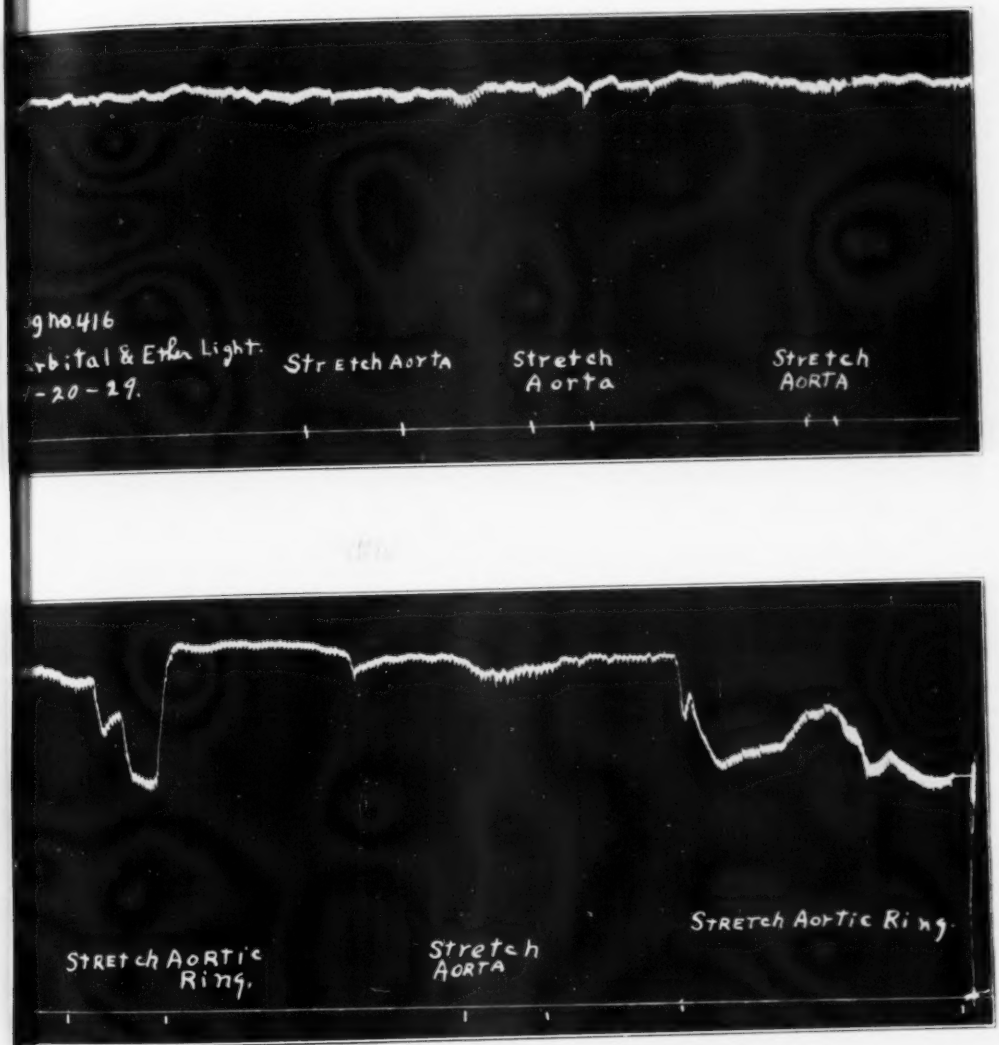

Fig. 13.—Curve for dog 416, showing absence of effect on blood pressure when aortic arch is stretched and marked effect when aortic ring is stretched (70 mm. mercury) at end; sudden death of dog occurred from blocking of coronary orifices.

Dog 416 A.—With the animal under light barbital anesthesia, the carotid artery was exposed and freed from the surrounding structures and incised for introduction of the dilator. The blood pressure was recorded by cannula in the right carotid. Stretching of the ascending portion of the aorta resulted in a slight fall of blood pressure (8 mm. of mercury). The instrument was passed on to the ring, but had stopped behind a cusp, and puncture of this cusp caused a fall in blood pressure (20 mm. of mercury). When the instrument was withdrawn and again passed into the ring (as recognized by its passing freely into the ventricle) and expanded, apparently the cusps were forced against the openings of the coronary artery, which produced immediate death (fig. 13). Dog 301 illustrates the effect of pressure on the posterior aortic cusps with a fall of blood pressure (42 mm. of mercury) (fig. 14).

Dog 418.—With the dog under barbital and light ether anesthesia, the carotid was exposed and the dilator introduced into the aorta. The blood pressure was

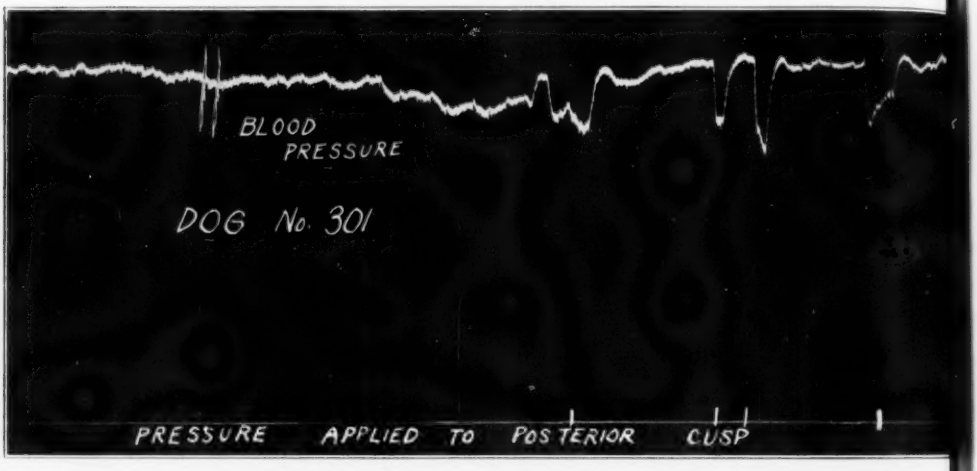

Fig. 14.—Effect on blood pressure of pressure applied to an aortic cusp.

recorded from the left femoral artery to eliminate the possibility that changes in the blood pressure might be due to interference in circulation of the carotid from which pressure had previously been taken. Repeated dilation of the arch and ascending aorta resulted in an increasing rise of blood pressure following each distention (8 to 26 mm. of mercury). When the instrument was passed into the ring and stretched, the coronary artery was accidently blocked, resulting in sudden death (fig. 15).

Dog 414.—With the animal under barbital anesthesia, the carotid artery was isolated for introduction of the aortic dilator, the blood pressure being recorded by cannula in the left femoral artery. Stretching of the arch and ascending aorta produced no change in pressure. Stretching of the aortic ring produced a fall in blood pressure (24 mm. of mercury). After severing of both vagi, stretching of the aortic ring produced a fall in blood pressure (fig. 16).

Dog 417.—With the dog under barbital anesthesia, the carotid artery was isolated for introduction of the aortic dilator, the blood pressure being recorded by

Fig. 15.—Curve for dog 418. Note increasing rise in blood pressure following repeated dilations of the arch of the aorta (highest, 30 mm. mercury).

cannula in the left femoral artery. Stretching of the aorta produced no change in blood pressure; stretching of the ring produced a fall (60 mm. of mercury). After severance of both vagi only a slight fall in blood pressure occurred as a result of dilating the ring (14 mm. of mercury).

Dog 416.—With the animal under barbital and light ether anesthesia, the carotid artery was isolated for introduction of the aortic dilator, blood pressure being recorded by cannula in the left femoral artery. Stretching of the ascending portion of the aorta and arch produced no fall in blood pressure. Stretching of the ring produced a fall (56 mm. of mercury). During another stretching of the ring, the coronaries were accidently occluded, resulting in death.

Dog 415.—With the dog under light ether anesthesia, the carotid artery was isolated for introduction of the aortic dilator, the blood pressure being recorded by cannula in the left femoral artery. Stretching of the ascending portion of

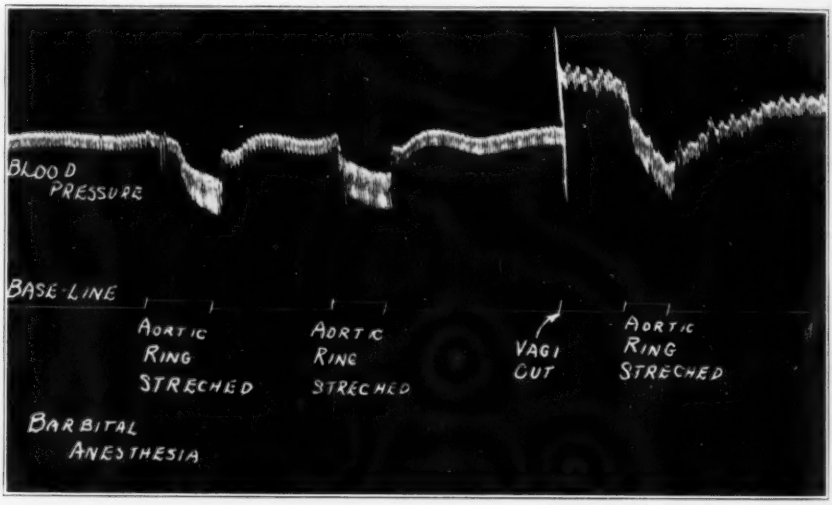

Fig. 16.—Curve for dog 414, showing effect of dilation of aortic ring and effect after severing the vagi.

the aorta and arch produced a rise (12 mm. of mercury) in blood pressure once. Later dilations had no effect. Stretching of the aortic ring produced a fall (40 mm. of mercury). Removal of the annulus of Vieussens and stretching of the ring produced a fall in pressure (58 mm. of mercury). Stretching of the arch produced a fall (8 mm. of mercury).

Dog 27.—With the animal under light barbital anesthesia, the carotid artery was isolated for introduction of the aortic dilator, the blood pressure being recorded by cannula in the left femoral artery. On the first stretching of the aorta, one of the springs broke, producing a slight perforation of the arch of the aorta. This resulted in a marked rise in blood pressure (77 mm. of mercury) and great stimulation of respiration, followed by the rapid death of the animal (fig. 17).

Dog 32.—With the dog under barbital anesthesia, the carotid artery was isolated for introduction of the aortic dilator, the blood pressure being recorded

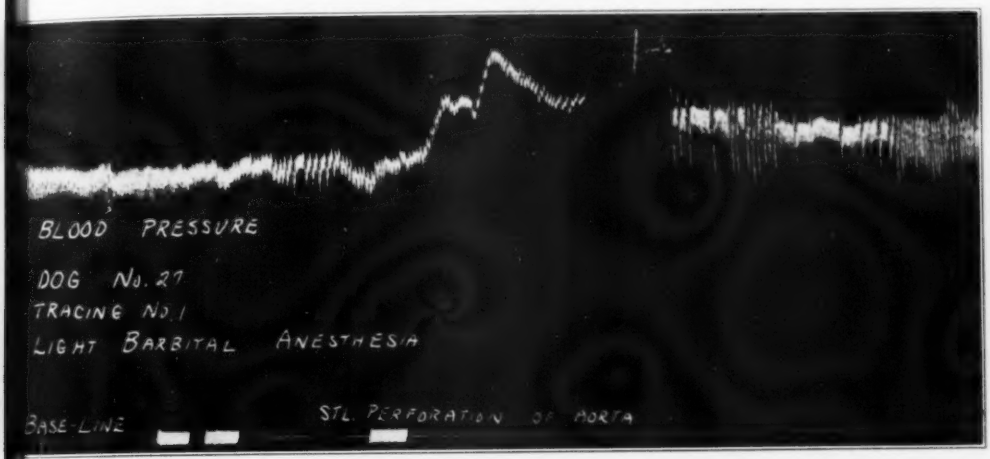

Fig. 17.—Curve for dog 27, showing effect of slight perforation of the aorta on blood pressure.

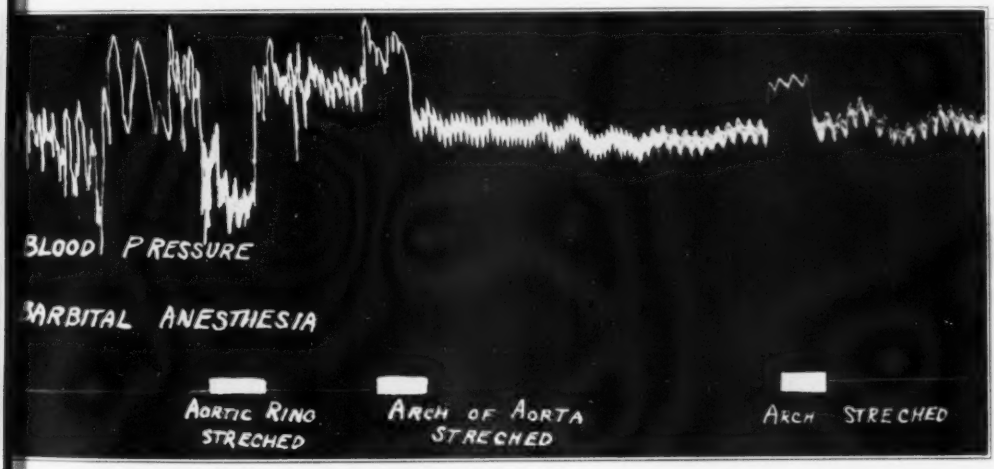

Fig. 18.—Curve for dog 430. Note prompt fall in blood pressure on stretching aortic ring and prompt return to normal following release of pressure. Note prompt rise in blood pressure when arch is stretched and also prompt fall on release of pressure.

Fig. 19.—Curve for dog 60, showing effect of traction on the cordae tendineae. Continuous traction after section of the vagi and later the sympathetics caused death.

by cannula in the left femoral artery. Stretching of the ascending portion and arch produced no change in blood pressure. After section of the vagi, no changes in blood pressure followed when the aorta was stretched, and a fall (30 mm. of mercury) occurred when the ring was stretched.

Dog 430.—With the animal under barbital anesthesia the left carotid artery was isolated for introduction of the aortic dilator, the blood pressure being recorded from the right carotid artery. Stretching of the ascending portion of the aorta produced a prompt rise in blood pressure of 26 mm. of mercury, with a prompt fall on release of pressure. Stretching the aortic ring caused a fall of 80 mm. of mercury (fig. 18).

Dog 60.—With the dog under barbital anesthesia, this animal was prepared as was dog 601. When the dilator was passed into the cavity of the left ventricle, one of the springs broke. Attempts to withdraw the instrument resulted in its becoming entangled with the chordae tendineae of the mitral valve. The marked effect on blood pressure resulting when traction was made on the chordae tendineae is shown in figure 19. The sympathetic was cut, following which traction was again made with a fall of blood pressure which persisted, causing the death of the animal.

SUMMARY

Effects of Stretching the Aorta, Aortic Ring and Ventricular Cavity on Pain and Respiration.—It is found that pain is not produced (1) by insertion of an instrument into and stretching of the carotid artery; (2) by sufficient pressure to pierce the aortic wall when obstruction is met at the junction of the carotid and aorta; (3) by passing the instrument into the ascending aorta and stretching it sufficiently to cut the intima; (4) by passing the instrument into the aortic ring, and (5) by perforation of the aorta, which has occurred a number of times from the breaking of the dilator spring; it does not result in pain until a sufficient quantity of blood has collected in the mediastinum to produce much stretching of the limiting tissues.

It is found that dyspnea follows stretching of the ascending aorta, aortic ring and left ventricle. This dyspnea is variable in degree, depending on the amount of stretching.

Effects on Blood Pressure of Stretching the Aorta, the Aortic Ring and the Ventricle (Preliminary Observations).—The universal acceptance of a depressor nerve would lead one to expect a fall in blood pressure when the aortic ring, ascending aorta or arch are dilated. Because of the finding of an isolated depressor nerve in rabbits, it has been presumed that depressor fibers are present in the vagus in all higher forms of animal life, including man. In no instance has dilatation of the ascending aorta produced a definite fall of blood pressure that would indicate the stimulation of a depressor nerve. On the other hand, in two cases (dogs 418 and 430) there was an immediate definite rise in blood pressure (26 mm. of mercury) which lasted during the period of stretching and promptly returned to normal on release of

pressure. The reflex producing this rise in blood pressure is affected by anesthesia and by the variation in dogs.

As soon as this observation was made, a careful study of our clinical cases of aortitis, with and without aortic insufficiency, has shown hypertension above 150 mm. of mercury systolic pressure to be present in 40 per cent (thirty-four cases).

Dumas [9] reported three cases of abdominal aortitis and one of thoracic aortitis in which there were paroxysms of hypertension, dyspnea and precordial pain. He explained these symptoms as being due to a functional constriction of some portion of the arterial system.

Stretching of the aortic ring produces a prompt fall in blood pressure which is proportional to the amount of tension. The fall in pressure occurs promptly and disappears just as promptly on release of tension. Section of both vagi and the left sympathetic has no constant appreciable effect, although in dog 417 severing both vagi resulted in a decrease in the fall. In dog 415 severance of the left sympathetic connections did not affect the fall. The evaluation of the mechanical effect on blood pressure of producing so great and sudden insufficiency of the aortic ring appears impossible.

Perforation of two cusps does not have so great an effect on the fall of blood pressure as does the distention of the aortic ring with the dilator. Pressure on a cusp (dog 301) probably does not cause a material aortic insufficiency, and yet produces a definite fall in blood pressure. It seems that the fall in pressure depends on a factor other than that of mechanical interference with normal blood flow, but further evidence is required to settle this point. This is also true of the fall in pressure on pulling on the chordae tendineae.

Stretching of the abdominal aorta in one experiment caused a rise in blood pressure.

Effects of Stimulation of the Annulus of Vieussens.—When the annulus of Vieussens was being severed, a marked rise in blood pressure was recorded. After severance of all connections with the vagus, repeated mechanical and electrical stimulation produced constant rises in blood pressure. Since this observation was made, Leriche and Fontaine [10] have reported similar observations.

CONCLUSIONS

1. Acute mechanical distention of the aortic arch, ascending aorta, aortic ring and the cavity of the left ventricle does not produce pain in the dog.

9. Dumas, A.: Paroxysms of Hypertension and Pain in the Course of Aortitis, J. de méd. de Lyon **9**:699 (Dec. 5) 1898.

10. Leriche, Rene, and Fontaine, Rene: Contribution to the Physiology of the Annulus of Vieussens, Arch. d. mal. du cœur **4**:215 (April) 1929.

2. Acute mechanical distention of the parts of the aorta and heart named produces paroxysmal dyspnea.

3. Acute mechanical distention of the ascending aorta and aortic arch at times produces either a rise in blood pressure or no definite change.

4. Acute mechanical distention of the aortic ring of the left ventricle invariably produces a fall in pressure even when both vagi are severed.

5. Mechanical and electrical stimulation of the annulus of Vieussens after all vagal strands are severed invariably produces an increase in blood pressure.

6. According to the experimental evidence given in this paper, the only mechanism for the production of cardiac pain is that of lessened blood flow to the myocardium.

BUNDLE BRANCH BLOCK

THE PHENOMENON OF ITS DEVELOPMENT IN RELATION TO AXIS DEVIATION OF THE HEART *

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The difficulties experienced in differentiating between simple left axis deviation of the heart and beginning right bundle branch block are known to all clinicians interested in cardiovascular pathology. Observers of wide experience have noted from time to time that what appeared to be a simple left axis deviation of the heart at one electrocardiographic examination might subsequently and within a short time prove to be a true right bundle branch block.

During the past five years, we have observed a group of patients whose electrocardiograms showed certain common characteristics. In some of these patients complete right bundle branch block developed; in one of them, the condition started with what appeared to be a right axis deviation of the heart, and at death the electrocardiogram showed a left bundle branch disturbance.

A consideration of the earliest manifestations of bundle branch block forms the basis of this paper. The cases selected were chosen without regard to etiology or clinical diagnosis; they were taken solely because of the similarity of their tracings.

The subject of bundle branch block is not new; the experiments of Eppinger and Rothberger,[1] Eppinger and Stoerk,[2] Rothberger and Winterberg,[3] and others have clarified the chain of events that brings about the characteristic electrodynamic disturbances of the heart which are now easily recognized as being associated with pathologic changes existing in the main branches of the conducting system. The accepted criteria of bundle branch block have been briefly outlined by Carter,[4] Lewis[5] and others. The principle characteristics may be stated as

* Submitted for publication, Nov. 8, 1929.

1. Eppinger and Rothberger: Ztschr. f. klin. Med. **70**:1, 1910.
2. Eppinger and Stoerk: Ztschr. f. klin. Med. **71**:157, 1910.
3. Rothberger and Winterberg: Zentralbl. f. Herzkrankh. **5**:206, 1913.
4. Carter, E. P.: Clinical Observations on Defective Condition in the Branches of the Auriculoventricular Bundle, Arch. Int. Med. **13**:803 (May) 1914.
5. Lewis, T.: Heart **4**:242, 1913.

follows: 1. A delay in the QRS complex occurs beyond 0.10 second. 2. The amplitude of the QRS complexes is usually increased. 3. The QRS complexes are notched, split or feathered. 4. The ventricular complex is generally diphasic; the QRS complex is in the opposite direction to the T wave. 5. The direction of the QRS complex in leads I and III determines the bundle branch which is involved.

Of these five characteristics, probably more attention has been devoted to the first than to any of the others. Before mere delay of transmission time of the QRS complex can be determined, the normal time relationship must be established. One finds no general agreement as to this figure; Lewis [6] stated that from 0.03 to 0.04 is normal. Einthoven,[7] in a comparative study, expressed the belief that 0.03 is the normal time in most mammalian hearts. On the other hand, Kraus and Nicolai expressed the opinion that 0.06 second is more common. Oppenheimer and Rothschild [8] considered that these figures must be more flexible, and that transmission times as high as 0.1 second may be within normal limits. Wilson and Herrmann,[9] in an exhaustive study, found that a delay of 0.1 second or over was the most important indication of the existence of a bundle branch disturbance. These authors have shown that the QRS complex may be modified in two ways: (1) by prolonging the time required by the excitation process to reach all parts of the ventricular muscle and (2) by changing the course of the excitation wave and thus also the order in which the various muscle regions pass into the active state.

Both these factors are important, for since the conducting systems of the two ventricles are not linked together except through the main stem of the bundle of His, the impulse can reach the ventricles affected by the lesion only by passing through the intraventricular septum and the adjacent muscular structures of the heart. The rate of the transmission of the impulse through such tissue is very slow. The point at which the impulse enters the Purkinje plexus of one or the other ventricle will determine to a considerable extent the order in which the various areas of the endocardial muscles of that ventricle are activated. In other words, the form and the duration of time exhibited by the QRS complex are apparently dependent on the new course assumed by the excitation wave as it passes through the ventricular muscle in order to complete its journey. Assuming that the QRS interval is

6. Lewis, T.: Clinical Electrocardiography, London, Shaw & Sons, 1924, vol. 3, p. 22.

7. Einthoven, W.: Arch. f. d. ges. Physiol. **149**:65, 1913.

8. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement, J. A. M. A. **69**:429 (Aug. 11) 1917.

9. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, Arch. Int. Med. **26**:153 (Aug.) 1920.

equal to the time during which the excitation wave is spreading plus the time required by the last muscle region activated to develop its full potential, it can be readily determined to what extent the first factor has been changed as the second is practically constant and of very brief duration (0.0085 second).

The course of the excitation wave as it spreads through the ventricles has been demonstrated by many observers. Entering the special conduction system of the ventricles by way of the bundle of His, it passes along the two chief branches of this structure and then frequently subdivides and terminates in the Purkinje system which lines the endocardial surface of both chambers. From the Purkinje plexus it spreads outward through the ventricular walls toward the epicardial surface of the heart. Wenckebach and Winterberg [10] demonstrated with great accuracy the speed at which this impulse passes through the various portions of the heart; they have shown that the excitation process passes almost ten times as fast through the specialized pathway of conduction as through a new myocardial pathway.

There is still some discussion in regard to the continuity of the Purkinje system in the human heart; in the dog and the horse the system seems to be rather readily demonstrated, but there has never been a complete visualization of the entire system in man. Assuming, however, that the Purkinje fibers in the human heart resemble those of the laboratory animals, Lewis stated that in right bundle branch block the first part of the QRS complex is written by the spread of the excitation process in the left ventricle by way of the combined pathways of myocardium and Purkinje network; on the other hand, in left bundle branch block the QRS complex is written by a similar spread through the right ventricle.

Another factor concerned in prolongation of the QRS interval is unquestionably the retarded spread of the excitation wave through the intraventricular septum. Willius [11] has pointed out that the thickness of the septum may therefore have much to do with the delay in the transmission of the impulse; when the septum is very thick, as in greatly hypertrophied hearts, the delay is longer than in thinner septums uninvolved with such pathologic changes. In considering the relative frequency of right and left bundle branch block, many observers have suggested that the relative rarity of the latter condition is purely anatomic in origin, since the right main bundle is situated very superficially to the endocardium of the papillary muscles of the right side of the heart, and hence is more accessible to damaging proc-

10. Wenckebach and Winterberg: Unregelmässige Herztätigkeit, Leipzig, Wilhelm Engelmann, 1927, p. 87.

11. Willius, F. A.: Am. Heart J. **1**:577, 1926.

esses. It is generally believed that even small areas of cardiac disease in this area may give graphic evidence of a delayed QRS interval; widespread damage must be produced, however, in the region involving the left main bundle before there is evidence of this condition.

Recently, Luten and Grove[12] studied the development of bundle branch block from its beginning; in a series of 237 cases showing left axial deviation of the heart with altered T waves in the first lead, subsequent evidences of right bundle branch block were shown. They expressed the belief that the condition is closely associated with hypertensive heart disease with accompanying myosclerotic changes.

Reviewing carefully cases showing a left axial deviation of the heart, we have selected a group with tracings having the characteristic QRS and T wave positions of right bundle branch block but without the QRS delay. In other words, of a group of 469 cases showing left axial deviation of the heart we have picked 46 that show an upright QRS and a negative T wave in the first lead and a downward QRS and an upright T wave in the third lead. These cases have been followed for periods ranging from eight months to four years. Of the 46, 21 developed true right bundle branch block with no change of sinus rhythm and 8, auricular fibrillation with bundle branch block; 4 showed complete auricular and ventricular dissociation with bundle branch block, and the remaining 13 showed right bundle branch block with an extrasystolic arrhythmia from single and multiple foci. In this connection, we have been able to watch one case of right axis deviation of the heart which developed into a true left bundle branch block prior to the death of the patient. This case is interesting in that it showed in every respect the reverse observations of those seen in the other group of cases.

We have selected one case from each of the four types mentioned in right bundle branch block.

REPORT OF CASES

Case 1.—A widower, aged 56, a laborer, had a long history of hypertensive heart disease. At the age of 40 he was rejected for life insurance; at 51 he was known to have a blood pressure of 210 systolic and 105 diastolic. Three years later, he began to have symptoms of dyspnea, palpitation and substernal distress even on mild effort. Electrocardiographic studies made at that time (fig. 1*A*) showed a left axial deviation of the heart with a QRS complex measuring 0.08 second: T1 was diphasic. Physical examination revealed a heart that was not very large in spite of his long history of hypertension. The patient was seen again fifteen months later (fig. 1*B*), and the electrocardiogram was unchanged except for a slight slurring in the second limb of the QRS complex. The T wave seemed to be more inverted and less diphasic than before. A third examination was made about ten months later (fig. 1*C*); at this time, there was well marked

12. Luten, D., and Grove, E.: Am. Heart J. **4**:431 (April) 1929.

evidence of a complete right bundle branch block. The QRS complex was now delayed to about 0.18 second; it was split and feathered, and the T wave in lead I was completely inverted. The patient died two weeks later during an acute attack of pulmonary edema.

CASE 2.—In a woman, aged 49, the previous cardiovascular history was essentially negative. One year prior to the first examination (fig. 2*A*) she began to complain of dyspnea and general weakness. She was seen by us for the first time at the age of 46; at that time, she showed a well marked left axial deviation of the heart with a diphasic T wave in the first lead and an upright T wave in the third lead. The QRS complex measured 0.06 second. There was a normal sinus rhythm. Both the heart and the aorta were somewhat enlarged; the blood pressure was 140 systolic and 90 diastolic. She was seen again about eight months later, when she was referred back to us because of an irregularity of the pulse. An examination at this time (fig. 2*B*) showed that the irregularity was due to a nodal extrasystolic arrhythmia. The QRS complexes had widened to 0.1 second

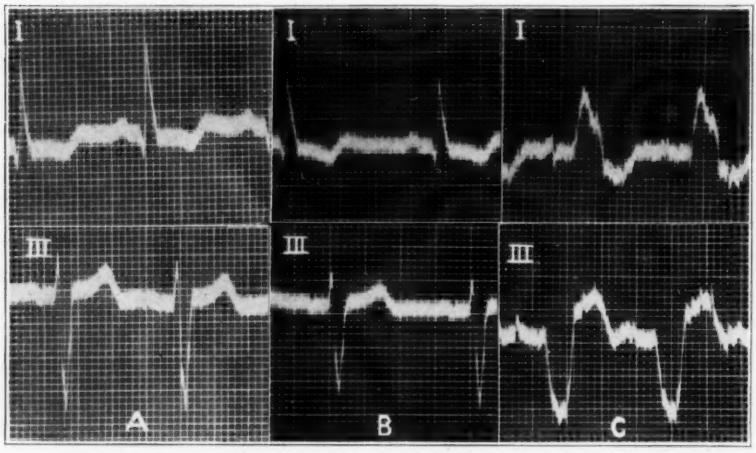


Fig. 1.—Typical development of pure right bundle branch block from a simple left axis deviation. Note the characteristic T wave alteration in lead I *A*.

and in the second limb of the complex both in the first and in the third leads, there were evidences of slurring. The T waves in the first lead had become more inverted, and those in the third lead more upright. She was seen again a year and a half later, this time with a well marked auricular fibrillation. The QRS complexes (fig. 2*C*) were now delayed to 0.12 second with notching, and the T waves were inverted in the first lead. The heart action became greatly decompensated, and the patient has been bedridden for the past year.

CASE 3.—A man, aged 62, had no previous cardiovascular history. He was beginning to complain of heart consciousness and palpitation, which were especially well marked after eating. He was being treated for gastro-intestinal symptoms when first seen. Electrocardiographic studies (fig. 3*A*) showed a well marked left axial deviation of the heart; the QRS complex was 0.08 second; the T wave in the first lead was definitely inverted, but in the third lead it was

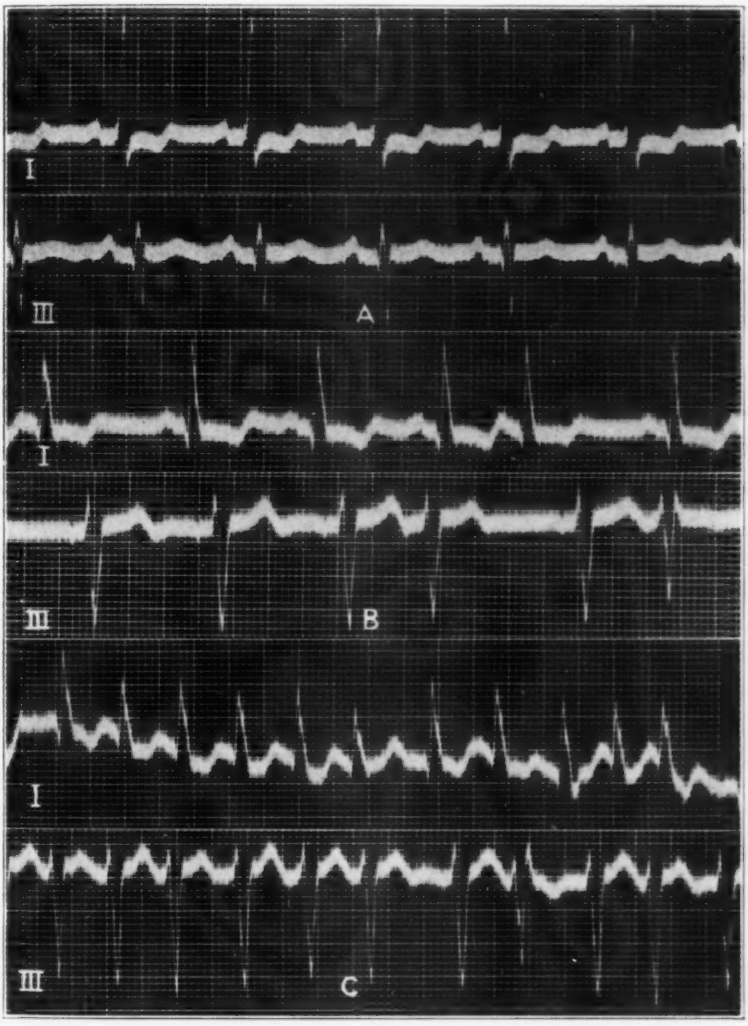


Fig. 2.—Development of auricular fibrillation with right bundle branch block twenty-six months after the appearance of left axis deviation.

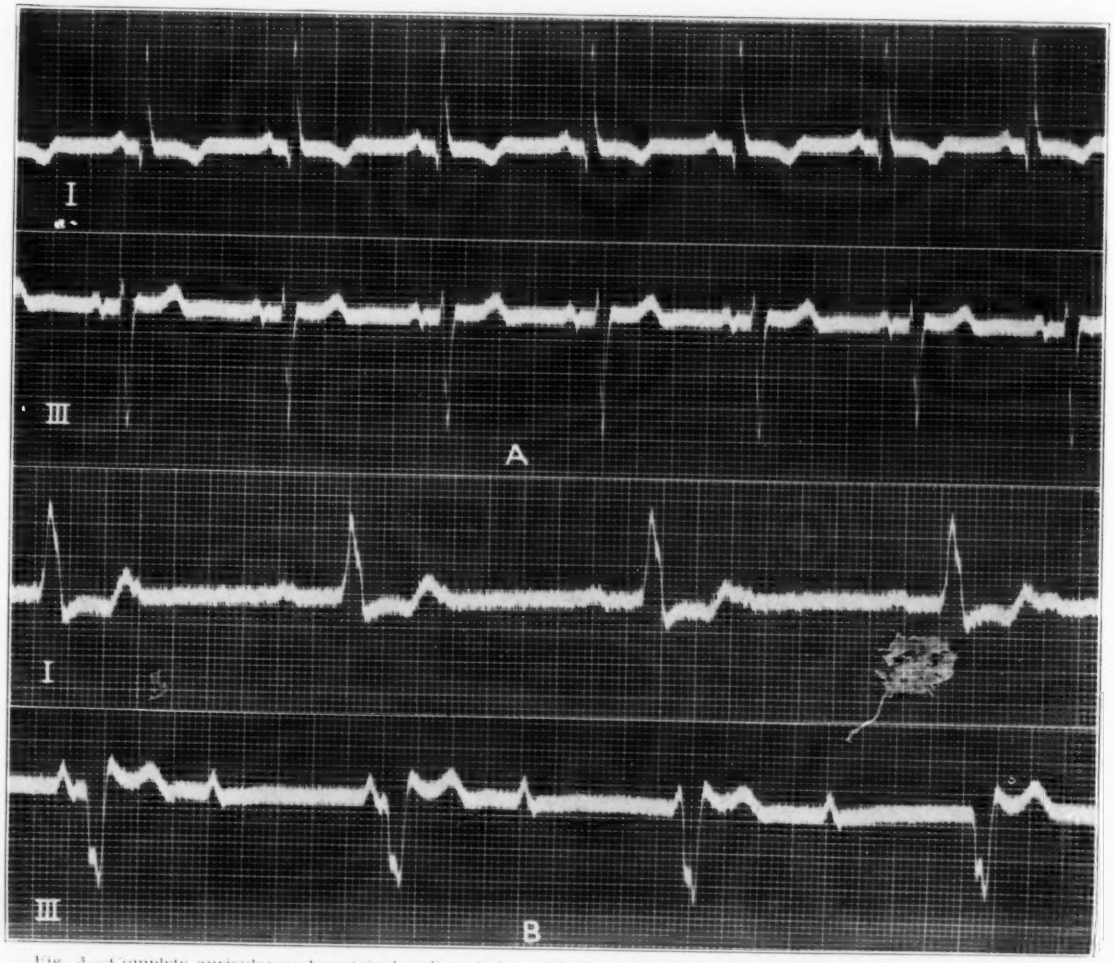


Fig. 3.—Complete auricular and ventricular dissociation with right bundle branch block developing two years after the

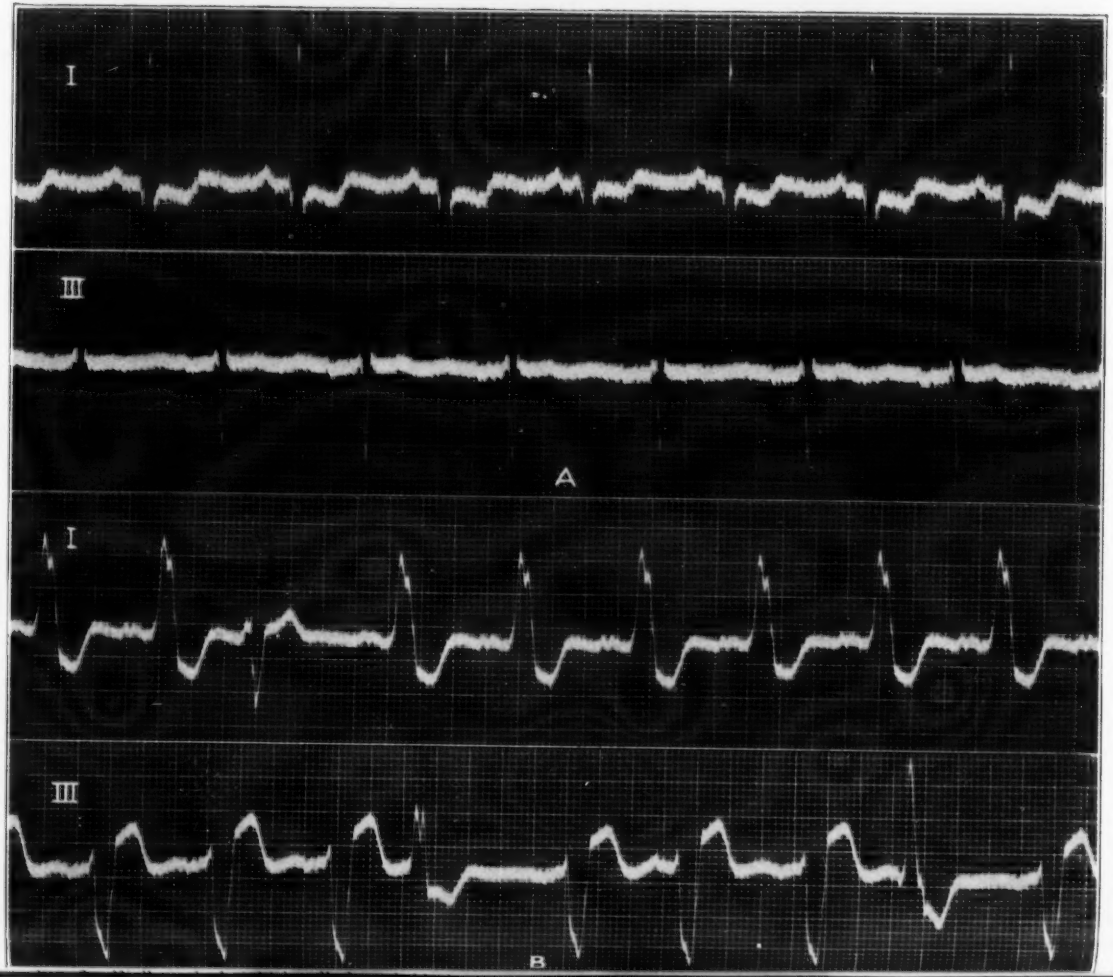
upright. About two years later, the patient was again seen because of a slow and irregular pulse. Studies made at that time (fig. 3*B*) showed a complete auricular and ventricular dissociation; a complete right bundle branch block had also developed. The QRS complex was now delayed to 0.14 second, and the complexes were split and feathered. The T wave in the first lead while downward was somewhat altered because of the superimposed P waves. One year after this record was taken, the patient was still alive.

CASE 4.—A man, aged 54, had a previous history of cardiovascular disease dating from a severe attack of toxic nephritis which occurred four years before. The blood pressure was 190 systolic and 100 diastolic; both the heart and the aorta were enlarged. On the first examination (fig. 4*A*), a marked left axial deviation of the heart was noted. The QRS complex measured only 0.06 second; the T waves of the first lead were inverted and diphasic but were upright in the third lead. The patient was seen again about fourteen months later; his condition had slowly became worse and he was dyspneic, showing congestive signs of heart failure. He also had an irregular pulse. Electrocardiographic studies (fig. 4*B*) showed the full development of a right bundle branch block, the QRS complexes were delayed to 0.14 second, and the complex was split and feathered. The T waves in the first lead were markedly inverted while in the third lead they were upright. The irregularity noted in the pulse was found to be an extrasystole which was apparently coming from shifting foci in the right ventricle. The patient died about three days after the record was taken.

In this connection it may be useful and interesting to consider the process in cases in which the electrocardiogram shows a right instead of a left axis deviation of the heart. Such cases are extremely infrequent, and may be relatively as rare as the occurrence of left bundle branch block itself.

CASE 5.—A man, aged 56, had a long history of chronic bronchitis, emphysema and asthma. On physical examination, he showed the typical changes in the lungs seen in chronic pulmonary and bronchial disease, with associated cardiovascular changes. The heart, however, was not greatly enlarged, and blood pressure levels were maintained at 110 systolic and 70 diastolic. Electrocardiographic studies showed a right axial deviation of the heart; the QRS complex measured only 0.06 second; the T waves were upright in the first lead but inverted in the third. Because of his pulmonary condition, the patient was advised to live in the southwest; he stayed in Arizona for about three and a half years and returned, apparently much improved. Electrocardiographic studies (fig. 5*B*) showed a fully developed left bundle branch block with a delay in the QRS complex to about 0.14 second. There was apparently no other change in the cardiovascular system. After several attacks of pulmonary edema, the patient died suddenly.

The first four typical cases have been taken from a group of 46, all showing more or less similar electrocardiographic studies. This group represents a little more than 10 per cent of the total number of cases in which a left axis deviation of the heart was found in the course of a routine cardiovascular examination. We believe that 10 per cent is too high a figure to be merely coincidental, and we agree with the observations made by Luten and Grove that left axis deviation of the bundle branch block configuration must be considered in a


I
III
A
I
III
B

more serious light than a mere axis deviation of the heart. There is a growing tendency among cardiographers to consider a left axis deviation perfectly normal during and after the middle age period. When such axis deviation is associated with T wave changes in the first and third leads resembling the bundle branch block configurations, such cases must be regarded as potential types that may subsequently develop into true conduction disturbances of the most serious significance.

No discussion of etiology has been considered here, for it can be assumed that this process is one of advancing myosclerosis as a result

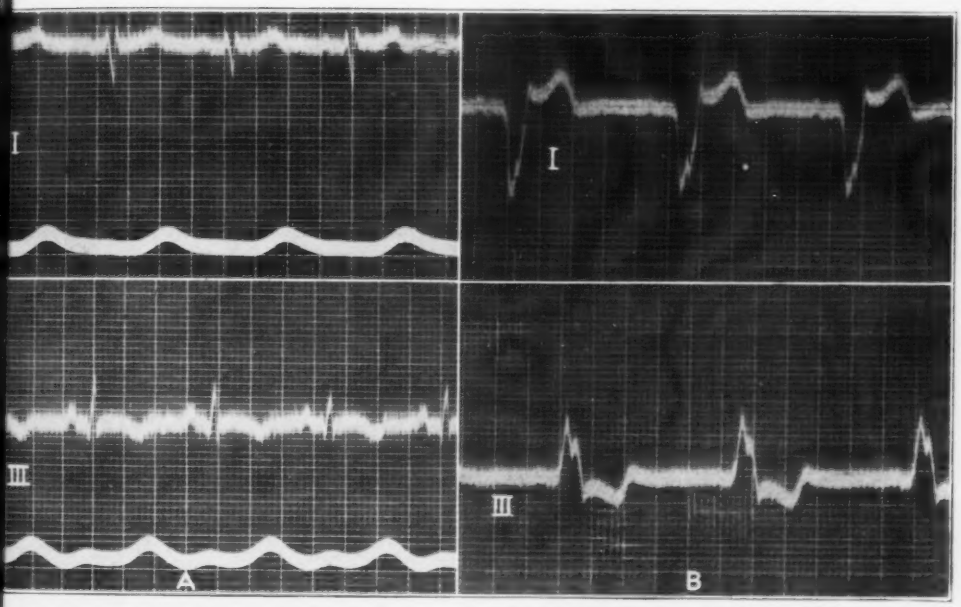


Fig. 5.—The development of a left bundle branch block from a previous right axis deviation, a relatively uncommon condition. Note that the tracings in lead I*A* and III*A* show a moderate right axis deviation with T wave alterations in the third lead similar to that seen in the previous figures in lead I.

of heart muscle damage or disturbances in the coronary arterial circulation. While it is true that frequently cases presenting clinical evidence of coronary thrombosis may show left axial deviation of the heart with alterations of the T waves in the first lead which in many respects may be similar if not identical with those seen in the configuration discussed, T wave alteration of the purely coronary type is usually found in more than one lead. In fact, many observers believe that

coronary disease cannot be determined from electrocardiographic tracings unless changes in the T waves are found in two leads.

The relative rarity of left bundle branch block presents many interesting considerations. In case 5 we have seen a right axis deviation of the heart develop into a true left bundle branch block prior to a very sudden death. The configuration of the first tracing is theoretically what might be anticipated if the process by which right bundle branch block develops is true. The downward QRS complex and the upward T wave in the first lead and the upward QRS complex and downward T wave in the third lead are but the reverse picture of that found in right bundle branch disturbance.

SUMMARY

Left axis deviation of the heart is so frequently found in middle and advanced age periods that many observers regard such an electrocardiographic manifestation as normal. We have been impressed by the fact that more than 10 per cent of our series of left axis deviations have been associated with alterations in the T waves of the first and third leads which are suggestive of the bundle branch block configuration. In a follow-up study of these cases we have found that a right bundle branch block has developed in from eight months to four years. Such cases have terminated in pure right bundle branch block without change of sinus rhythm, bundle branch block with auricular fibrillation, bundle branch block with complete auricular and ventricular dissociation and bundle branch block with extrasystolic arrhythmia of single or multiple foci. The common etiologic origin of these four terminal stages may cause any one of them to be found with the others, and the step from one to another may be due to gradual extension of the degenerative process in the heart muscle.

Considerable prognostic information may thus be secured from close scrutiny of all electrocardiograms taken during the age periods mentioned. The onset of bundle branch block may sometimes be suspected, many months and even years prior to the actual development of the typical delayed conduction phenomena which are so characteristic of this condition.

METABOLISM AND TREATMENT OF OSTEOMALACIA

ITS RELATION TO RICKETS *

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Although osteomalacia is a well recognized disease entity, complete metabolic studies using the newer nutritional methods are not available in the literature. An extremely advanced case of the disease recently observed by us over a period of one year offered an exceptional opportunity to study the disease and the effects of treatment.

HISTORICAL RÉSUMÉ

Pathology.—Various views have been held regarding the actual changes in the bones of patients with osteomalacia. Virchow [1] assumed that the inorganic part of bone was inert and without metabolism, and believed that osteomalacia was due to dissolution of the mineral constituents by an acid. Cohnheim [2] was the first to take exception to this view, asserting that even in adults, bones undergo active anabolism and catabolism. He believed that absorption of the organic and inorganic substances is accomplished in osteomalacia through the activity of the osteoclasts and that later new bone consisting of organic matrix free from lime salts is laid down. This concept of the nature of osteomalacia was strongly supported by the histologic studies of Pom-

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* From the Thorndike Memorial Laboratory of the Boston City Hospital, the Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School.

1. Virchow, quoted by von Recklinghausen, F.: Untersuchungen über Rachitis und Osteomalacie, Jena, Gustav Fischer, 1910.

2. Cohnheim, J.: Lectures on General Pathology, translated by A. McKee, London, New Sydenham Society, 1889.

mer [3] and Looser [4] and by the chemical and metabolic studies of McCrudden.[5] As a result of these studies, the condition is now generally considered to be the result of widespread softening and absorption of preexisting bone (halisteresis) and the formation of uncalcified new osteoid tissue.

Etiology.—While the studies of McCrudden demonstrate the nature of the pathologic changes in the bones in osteomalacia and the importance of pregnancy as a contributory factor, they do not throw light on the nature of the underlying causation. The more important etiologic theories concerning osteomalacia may be grouped under two headings: (1) Endocrine Abnormalities and (2) Vitamin Deficiency.

ENDOCRINE ABNORMALITIES

Parathyroid Dysfunction.—Certain authors have believed that osteomalacia results from dysfunction of the parathyroid glands because of their intimate relation to calcium metabolism. Some observers have considered that hyperparathyroidism leads to osteomalacia, while others have held hypoparathyroidism responsible. Erdheim [6] as early as 1917 commented on the frequent occurrence of enlarged parathyroid glands in patients with osteomalacia and believed that the hypertrophy represented an inadequate attempt at compensation. The alteration of the parathyroid gland was thus considered a result and not a cause of the disease. Hoffheinz [7] reported forty-five cases in which the patients had enlargement of one or more of the parathyroid glands. Of these patients, seventeen had osteitis fibrosa, eight had osteomalacia and two had rickets. Perretti,[8] acting on the assumption that parathyroid deficiency

3. Pommer, G.: Untersuchungen über Osteomalacie und Rachitis, Leipzig, 1885.

4. Looser, E.: Ueber Spätrachitis und die Beziehungen zwischen Rachitis und Osteomalacie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **18**:678, 1907-1908; Ueber Spätrachitis und Osteomalacie; Klinische, röntgenologische, und pathologisch-anatomische Untersuchungen, Deutsche Ztschr.f.Chir. **152**:210, 1920.

5. McCrudden, F. H.: A Study of the Metabolism in Osteomalacia, Am. J. Physiol. **17**:211, 1906; The Composition of Bone in Osteomalacia, ibid. **17**:32, 1906-1907; The Effect of Castration on the Metabolism in Osteomalacia, ibid. **17**: 211, 1906-1907; The Effect of Castration on the Metabolism, J. Biol. Chem. **7**: 185, 1909-1910; Studies of Bone Metabolism, Especially the Pathological Process, Etiology and Treatment of Osteomalacia, Arch. Int. Med. **5**: 596 (June) 1910. McCrudden, F. H., and Fales, H.: Studies in Bone Metabolism: The Etiology of Non-Puerperal Ostomalacia, Arch. Int. Med. **9**:273 (March) 1912.

6. Erdheim, J., quoted by Biedl, A.: Innere Sekretion, ed. 2, Berlin, Urban & Schwarzenberg, 1913, p. 108.

7. Hoffheinz: Ueber Vergrösserungen der Epithelkörperchen bei Ostitis fibrosa und verwandten Krankheitsbildern, Virchows Arch. f. path. Anat. **256**:705, 1925.

8. Perretti, V. R.: Il ricambio del calcio e gli estratti paratiroidei in un caso di osteomalacia, Riforma med. **43**:1062, 1927.

played an important rôle in the causation of osteomalacia, treated one patient with injections of a parathyroid extract and stated that it favorably affected the course of the disease.

Kerl [9] reported one case of extreme osteomalacia in which the parathyroid glands were markedly hyperplastic, but suggested that the histologic changes in the glands might be secondary to the skeletal disease. No pathologic changes were found in any of the other endocrine glands.

Sauer [10] suggested that undernutrition results in a suppression of the function of the parathyroid glands which, in turn, leads to a disturbance of lime salt metabolism resulting in malacia of the bones. Recently, Barr, Bulger and Dixon [11] demonstrated in man that hyperactivity of the parathyroid glands may be associated with decalcification of the skeleton, the clinical picture, however, being that of osteitis fibrosa cystica (von Recklinghausen's disease) rather than that of true osteomalacia. Similar cases have been reported by Wilder.[12]

Thyroid Dysfunction.—Morawiecka [13] observed a patient with osteomalacia in whom a profound disturbance of the thyroid gland was evident, and Koeppen [14] was likewise impressed by the relation between exophthalmic goiter and osteomalacia. These clinical observations are of interest in the light of the studies of Aub, Bauer, Heath and Ropes.[15] They demonstrated that patients with exophthalmic goiter excrete abnormally large amounts of calcium and phosphorus and show rarefaction of bones on roentgen examination.

Thymus Dysfunction..—Scipiades [16] reported an instance of osteomalacia which began during the patient's eighth pregnancy and progressed steadily for two years. The grafting of a thymus gland into

9. Kerl, F.: Zur Frage der Epithelkörperchenhyperplasien bei Osteomalazie und Osteoporose, Deutsche med. Wchnschr. **51**:1271, 1925; abstr., J. A. M. A. **85**:936 (Sept. 19) 1925.

10. Sauer: Hungerosteomalazie mit Tetanie, Deutsche med. Wchnschr. **45**: 1373, 1919.

11. Barr, D. P.; Bulger, H. A., and Dixon, H. H.: Hyperparathyroidism, to be published.

12. Wilder, R. M.: Hyperparathyroidism: Tumor of the Parathyroid Glands Associated with Osteitis Fibrosa, J. Endocrinol., to be published.

13. Morawiecka, J.: Un cas de maladie de Basedow associée à la sclérodermie et à l'ostéomalacie, Rev. neurol. **1**:217, 1928.

14. Koeppen: Ueber Knochenerkrankungen bei Morbus Basedowii, Neurol. Centralbl. **11**:219, 1892.

15. Aub, J. C.; Bauer, W.; Heath, C., and Ropes, M.: Studies of Calcium and Phosphorus Metabolism: III. The Effects of the Thyroid Hormone and Thyroid Disease, J. Clin. Investigation **7**:97, 1929.

16. Scipiades, E.: Erster durch Thymusimplantation geheilter Fall der Osteomalakie, Zentralbl. f. Gynäk. **48**:1885, 1924; abstr., J. A. M. A. **88**:1116 (April 12) 1924.

the abdominal wall of the patient resulted in the complete disappearance of the pains by the fourth day after operation. On the tenth day, the patient was able to walk. These clinical observations were made on the basis of experimental studies [17] that indicated a close resemblance between osteomalacia and the osteoporosis following thymectomy in dogs.

Khoor [18] described an extraordinary effect of the transplantation of a thymus gland from an infant, who had died of lobar pneumonia, into the rectus muscle of a 31 year old pregnant woman suffering from osteomalacia. Within seventeen hours of the transplantation, she gave birth to a normal female child. She improved rapidly, and left the hospital entirely symptom-free two weeks later.

Ovarian Dysfunction.—Fochier [19] in 1879 removed the ovaries and uterus in a patient with osteomalacia. He reported remarkable improvement, and advised oophorectomy as a curative procedure. Fehling [20] in 1894 reported the first series of cases in which the patients were treated by this method, and claimed extraordinarily favorable results. Cristofoletti [21] likewise ascribed the occurrence of osteomalacia to the abnormal persistence of ovarian function. McCrudden,[5] however, was unable to subscribe to the opinions of these authors, and, after reviewing the literature critically, reported that only a small percentage of cases showed evidence of cure. McCrudden performed numerous experiments on animals, as well as a detailed study of a patient before, a few months after and a year following oophorectomy and noted no important changes in calcium metabolism. He also raised a pertinent question, saying "if osteomalacia is due to overactivity of the ovaries, it is difficult to understand how a patient without ovaries can have osteomalacia."

Cramer,[22] however, in 1919 removed the ovaries of a pregnant woman with osteomalacia and reported that healing of the bones took

17. Scipiades, E.: Osteomalakiefälle, Zentralbl. f. Gynäk. **41**:953, 1917; Ueber Osteomalacie, Ztschr. f. Geburtsh. u. Gynäk. **81**:156, 1919.

18. Khoor, O.: Mit Thymus-Implantation behandelter Fall von Osteomalacie, Endokrinologie **2**:40, 1928.

19. Fochier, A.: Sur les modifications récentes de l'opération césarienne, à propos d'un cas d'amputation utéro-ovarienne comme complément de cette opération, Lyon méd. **31**:393, 473, 505 and 545, 1879.

20. Fehling, H.: Zehn Castrationen; Ein Beitrag zur Frage nach dem Werthe der Castration, Arch. f. Gynäk. **22**:441, 1884; Ueber Wesen und Behandlung der puerperalen Osteomalacie, ibid. **39**:171, 1891; Weitere Beiträge zur Lehre von der Osteomalacie, ibid. **48**:472, 1895; Ueber Osteomalacie, Ztschr. f. Geburtsch. u. Gynäk. **30**:471, 1894.

21. Cristofoletti, R.: Zur Pathogenese der Osteomalacie, Gynäk. Rundschau **5**:113 and 169, 1911.

22. Cramer: Zur Theorie und Therapie der Osteomalacie, Deutsche med. Wchnschr. **45**:475, 1919.

place with continuation of pregnancy. Gentili [23] ascribed the remarkable improvement in two patients with osteomalacia, one of whom had suffered for six years, to the oral administration of ovarian extract, although he also gave his patients calcium phosphate (amount not stated). Fraser [24] also maintained that osteomalacia is due primarily to ovarian hyperfunction.

Suprarenal Dysfunction.—Hoffmann [25] observed surprising clinical improvement following from five to ten hypodermic injections of epinephrine hydrochloride (1:1,000). Koltonski [26] was unable to alleviate his patient's condition by any treatment, including castration, until he injected epinephrine hydrochloride subcutaneously.

Edelmann [27] observed nineteen cases and stated that osteomalacia is related to a food deficiency and is precipitated in some persons by a pluriglandular disturbance. He injected epinephrine hydrochloride intramuscularly every three or four days, and believed that it caused the disappearance of pain and general clinical improvement.

Dayton [28] and Barrie,[29] on the other hand, observed no evidence of endocrine imbalance in the patients they studied. Similarly, Dock [30] found no evident endocrine abnormalities in sixteen cases, and Nadler [31] stated "there is no real evidence that the frequent and manifold endocrine manifestations occurring in osteomalacia are a cause rather than an expression of the same metabolic disorder."

VITAMIN DEFICIENCY

Scott [32] studied patients with osteomalacia in India, but was unable to discover any vitamin deficiency or other etiologic factor that might

23. Gentili, G.: Contributo clinico alla terapia e patogenesi dell'osteomalacia, Riforma. med. **38**:97, 1922; abstr., J. A. M. A. **78**:1427 (May 6) 1922.

24. Fraser, J. R.: The Ovary in Osteomalacia, Am. J. Obst. & Gynec. **14**:697, 1927.

25. Hoffmann, R.: Ueber eine gehäuft auftretende, deformierende Wirbelerkrankung und ihre Beziehungen zur Hunger-osteomalacie, Wien. Arch. f. inn. Med. **4**:91, 1922; abstr., J. A. M. A. **79**:1727, 1922.

26. Koltonski, H.: Ueber Osteomalacie, Monatschr. f. Geburtsch. u. Gynäk. **51**:253, 1920; abstr., J. A. M. A. **76**:1620 (Nov. 11) 1921.

27. Edelmann, A.: Ueber gehäuftes Auftreten von Osteomalacie und eines osteomalacieähnlichen Symptomenkomplexes, Wien. klin. Wchnschr. **32**:82, 1919.

28. Dayton, N. A.: Osteomalacia: Etiology and Report of a Case Occurring in an Imbecile with Psychosis, Boston M. & S. J. **188**:10, 1923.

29. Barrie, G.: Cancellous Bone Lesions, Ann. Surg. **61**:129, 1915.

30. Dock, G.: Osteomalacia, with a New Case, Am. J. M. Sc. **109**:499, 1895.

31. Nadler, W. H.: The Relation of the Endocrine Glands to Osteomalacia, Endocrinology **1**:40, 1917.

32. Scott, Agnes C.: A Contribution to the Study of Osteomalacia in India, Indian J. M. Research **4**:140, 1916; The Calcium Content of the Urine and Blood with Special Reference to Its Variation in the Condition of Osteomalacia, ibid. **4**:169, 1916.

be attributed to the diet. Hutchison and Stapleton,[33] on the basis of their experience in India, considered that osteomalacia and the type of rickets that occurs in adults are identical and that etiologic factors such as heredity, malaria, sanitation, early marriage and diet could be excluded. They pointed out that none of the great Indian famines was associated with late rickets or osteomalacia, although the food shortage was far greater than that in Vienna after the war. They considered lack of sunlight of greater importance, and pointed out that the seasonal incidence of "hunger malacia" in Vienna corresponded with seasonal changes in light, whereas there was no seasonal change in diet. They believed the lack of muscular activity in Indian women even more important than the lack of sunlight, especially since one patient became progressively worse in spite of daily exposure to sunlight.

Dalyell and Chick[34] reported that many patients in Vienna toward the end of 1918 complained of pains over the bones similar to that experienced in the early stages of osteomalacia. Marked improvement followed the administration of cod liver oil. No deformities of the bones were present in their subjects. Hume and Nirenstein[35] extended the studies of Dalyell and Chick and found that only 100 Gm. of cod liver oil was necessary to effect a marked clinical improvement. They believed that the disease was due primarily to a deficiency in fat-soluble vitamin. These authors stated, however, that they regarded the relation between hunger osteomalacia and the osteomalacia of pregnancy as quite uncertain.

Brenner[36] observed marked clinical improvement after the administration of phosphorus and cod liver oil to a patient with puerperal osteomalacia, and Higier[37] attributed the improvement in ten patients whom he treated similarly to the probable effect of vitamin A.

Miles and Feng[38] studied four cases of osteomalacia. Three of the patients received cod liver oil and improved, while one who received

33. Hutchison, H. S., and Stapleton, Grace: On Late Rickets and Osteomalacia, Brit. J. Child. Dis. **21**:96, 1924.

34. Dalyell, E. J., and Chick, H.: Hunger-Osteomalacia in Vienna, 1920: I. Its Relation to Diet, Lancet **2**:842, 1921.

35. Hume, E. M., and Nirenstein, E.: II. Comparative Treatment of Cases of Hunger-Osteomalacia in Vienna, 1920, as Out-Patients with Cod Liver Oil and Plant Oil, Lancet **2**:849, 1921.

36. Brenner, A.: Ueber Osteomalacie mit Epilepsy, Deutsche Ztschr. f. Chir. **176**:66, 1922; abstr., J. A. M. A. **80**:808, 1923.

37. Higier, H.: Endemie dysalimentärer Osteoarthropathie, Osteomalacie und Spätrachitis und ihre Stellung zur neuen Lehre von den Vitaminen oder Nutraminen, Ztschr. f. klin. Med. **500**:445, 1922; abstr., J. A. M. A. **80**:517 (March 17) 1923.

38. Miles, L. M., and Feng, C. T.: Calcium and Phosphorus Metabolism in Osteomalacia, J. Exper. Med. **41**:137, 1925.

olive oil did not improve. They performed excellent metabolic studies which indicated that osteomalacia as observed in China is a disease due to vitamin deficiency.

Goldstein [39] treated a male patient for severe osteomalacia with a vitamin preparation containing irradiated ergosterol; he also irradiated the patient with ultraviolet light and observed considerable clinical improvement. No studies of calcium and phosphorus metabolism were carried out.

Starlinger [40] observed conspicuous clinical improvement in a patient with osteomalacia following the administration of ergosterol.

It is evident from this brief résumé of the literature on osteomalacia that there are several forms of osteomalacia, and that the incidence, the clinical manifestations and the cause of the condition vary greatly in different parts of the world. The clinical and metabolic study of an American woman suffering from advanced and well defined osteomalacia herewith reported may be of assistance in the understanding of some of the problems concerning this disorder.

REPORT OF CASE

History.—Mrs. H. P., white, an American housewife, 38 years of age, was admitted to the Boston City Hospital on May 6, 1928, complaining of weakness, pains and tenderness over the bones and chest of two and a half years' duration.

There was no familial history of chronic bone disease, insanity, cancer, tuberculosis, diabetes or other disorder. Her father was killed in an accident at the age of 65. Her mother died at the age of 72, of an unknown cause. One brother was living and well; one was killed in the war. One sister died at the age of 17 of pneumonia.

It has been impossible to secure a complete marital history of the patient. She lived for some time in a remote city from which no report could be obtained. It is known, however, that she had had four alliances, which resulted in seven children, born twenty-four, twelve, eleven, ten, seven, five and two and a half years previous to her admission to the hospital. She had never had any miscarriages. She felt well throughout the pregnancies, had easy labors and was able to be up about the second day after delivery. Her last pregnancy, however, proved more difficult and marked the onset of her present illness. All living children were well, but the youngest child had evidences of rickets.

The patient slept well, getting an average of eight hours' sleep. Her household duties kept her rather confined to the house. She never took more than two cups of coffee and one cup of tea daily and was not addicted to alcohol or drugs. She ate red meat twice daily and a moderate amount of fresh green vegetables.

39. Goldstein, J.: Männliche Osteomalacie und Vigantol, Wien. klin. Wchnschr. **42**:202, 1929.

40. Starlinger, W.: Ueber die Beeinflussung des Verlaufes einer schweren Osteomalacie durch bestrahltes Ergosterin, Deutsche med. Wchnschr. **53**:1553, 1927.

She usually ate two apples and a pear every day, but did not like milk and took it rarely. She used little butter and never ate eggs or oranges. She usually ate cooked cereal once a day and average amounts of sugar, salt and condiments.

She never had severe headaches, vertigo or throbbing nor had she suffered injuries to her head. Her eyesight had always been good. She had never had any difficulty with her ears, nose or throat. Her teeth had never given her any trouble before her last pregnancy; then they caused considerable annoyance. Several loosened and fell out, while others developed large cavities and broke off. There had been no cardiorespiratory symptoms. Her appetite had always been good. Her bowels had always moved daily, and she never had been troubled with any gastro-intestinal symptoms. There had been no nocturia, frequency of urination or burning micturition. She had contracted syphilis twelve years previously and had received intensive treatment. Her Wassermann reaction, ten years previously, had been negative. Catamenia had begun when she was 8 years of age, had always followed a thirty-day cycle and was not associated with pain. The flow, which was not excessive, lasted from four to five days. Her last catamenia was one week before admission.

There had been no fainting spells, muscular twitchings or paresthesias. Her memory was good.

Her best weight had been about 135 pounds (61.2 Kg.), four years previously. On admission to the hospital, she weighed 86½ pounds (39.2 Kg.).

Present Illness.—The patient dated the onset for her present illness from the birth of a full time baby on Jan. 26, 1926, two and a half years before admission, although, as stated, she had felt far from well during the entire course of her pregnancy, experiencing generalized pains and aches, particularly during the final months. The birth was precipitous, but she did not lose much blood. On the third day after delivery, she left bed, against the advice of her physician and district nurse, and noticed that she failed to "pick up" as quickly as after previous pregnancies. She felt extremely weak, and on attempting to do her housework was forced to rest every few minutes. She continued, however, to nurse the baby.

Two years before admission, she noticed pain and a tight feeling around the left hip. A swelling then appeared in that region, which gradually increased in size and finally involved the lower part of the abdomen. A physician whom she consulted said that she had a "false pregnancy," but her periods remained perfectly regular. After seven months or seventeen months before admission, the swelling began to diminish and finally disappeared. She then felt fairly well for about a month. Generalized pains and aches returned, however, and for the next nine months she was unable to attend to her household duties on account of weakness and increasing discomfort. Seven months before admission, while putting one of her children to bed, she suddenly felt numb all over and moved with difficulty. Her left side felt especially weak, and she was unable to move the left eyeball. Her physician said that she had had a shock and ordered her to bed for three weeks. At the end of this time, she felt a little better, but was extremely weak. Six months before admission, she noticed that she was becoming shorter and that her back was humped. On her own initiative, she began to take 1 tablespoonful of fresh, unrefined cod liver oil twice a day, on alternate days. She became progressively weaker and was finally unable to leave bed. All her bones ached so much that she was unable to remain in one position for any significant length of time. Three months before admission to the hospital, she developed excruciating pain in the left side of the chest. The ribs on that side

seemed to her to have caved in and were so tender that she could not touch herself or lean back in bed without its causing great pain. Her chest felt tight and narrow, and excruciating pains appeared in both shoulders, legs and spine. Because of her extreme helplessness and the excruciating pain, she was forced to enter the hospital.

Physical Examination.—The patient was a deformed, extremely emaciated, young, white woman, lying in bed, mentally clear, but evidently in great pain. The skin was a dull, pasty white. The head was symmetrical, with no exostoses or depressions. The scalp showed no scars, but was tender over the occipital region. The hair was dark, plentiful and of normal texture. The eyes seemed prominent because of the emaciation of the face. The sclerae were strikingly blue; the conjunctivae, pale. The pupils were equal and regular, and reacted actively to light and accommodation. There was no exophthalmos, nystagmus or lid-lag. Joffroy's sign was negative. There was no ptosis. The extra-ocular movements were normal. By finger tests, the visual fields showed no gross abnormalities. Ophthalmoscopic examination showed pale fundi, no fresh or old hemorrhages, normal vessels and clearly outlined disks. The ears presented no deformity or discharge, and the drums appeared normal. The nose showed no discharge or obstruction. The lips were dry and slightly bluish. The mucous membranes were pale. The teeth were grayish rather than white and showed extensive necrosis and caries. Many were loose and showed large cavities. There was extensive pyorrhea of the gums, especially anteriorly. The tongue was smooth, shiny and slightly atrophic, and protruded in the midline without tremor. The throat was clear. The thyroid was palpable and prominent, but no thrill or bruit was present. There was no adenopathy. The thorax was conspicuously deformed and asymmetrical, showing marked flaring of the costal margins and an extensive depression in the left side of the chest, extending from the left axilla anteriorly to the midclavicular line. There was a thoracic scoliosis on the left and compensatory lordosis of the lower thoracic and lumbar vertebrae. The ribs could not be felt over the depression in the left anterior side of the chest. Palpation of the thorax was generally unsatisfactory because of the exquisite tenderness. The respiratory expansion was markedly limited. Laterally, the lower costal margins almost touched the iliac crests. The cardiac impulse was forceful and was seen and felt in the fifth left interspace, 7.5 cm. from the midsternal line. The right border of dulness was not made out because of the tenderness. The heart sounds were of good quality, and there was a soft systolic murmur at the apex. The rate was 90, and the rhythm was regular. Neither the arteries nor the veins showed sclerosis. The radial pulses were equal and regular; the rate, 88. The blood pressure was 110 mm. of mercury systolic and 70 diastolic. The lungs were clear and resonant throughout, except at the right lower part of the back, where the breath sounds were harsher than normal. The abdomen was level and the abdominal wall was extremely thin and atrophied, showing many transverse folds when the patient sat or stood up. There was no tenderness or spasm. No masses were felt, and the liver, spleen and kidneys were not palpable. The iliac crests were exceedingly prominent, especially on the right. The symphysis pubis was prominent, "beaked" and exquisitely tender. The results of the rectal examination were negative. A gynecologic consultant reported, "Multiparous introitus, moderately relaxed pelvic floor, and bilaterally scarred cervix. Uterus in good position and normal in size. Vaults negative. Marked tenderness of symphysis pubis." Both upper and lower extremities showed marked atrophy of the soft tissues and exquisite tenderness on pressure. There were no apparent fractures. The left thigh and leg were tender and pain-

ful, particularly on motion. No edema, varicosities, deformities or clubbing were present. The superficial reflexes were normal, while the knee and ankle jerks were increased. There were no Kernig, Babinski, Trousseau or Chvostek signs. There was no ataxia, except that the left arm moved somewhat unsteadily and jerkily in the finger to nose test. The position sense was good. There was a moderate scoliosis and lordosis of the thoracic spine. The patient weighed 86½ pounds (39.2 Kg.) and was 59¼ inches (150.6 cm.) in height.

Clinical Pathologic Examination.—The hemoglobin was 60 per cent (Newcomer). The red blood cell count was 3,500,000, and the white blood cell count, 8,000 per cubic millimeter. The differential white blood cell count per hundred cells was: polymorphonuclear neutrophils, 60; polymorphonuclear eosinophils, 2; lymphocytes, 35; monocytes, 3. The red blood cells were slightly but definitely achromic and showed slight poikilocytosis and anisocytosis. The reticulocytes were sparse. The icteric index was 4. The Kahn and Wassermann reactions of the blood were negative on four successive examinations. The urine was normal. The basal metabolic rate was +6 per cent.

Roentgenologic Examination.—The roentgenologic examination by Dr. Max Ritvo showed a "marked degree of lime absorption with diminished density of all the bones and marked thinning of the cortex. There is a marked scoliosis to the left in the dorsal region. The ribs on the right side are collapsed, angulated, and the interspaces are very markedly narrowed. The epiphyses of the long bones show the same degree of lime absorption and thinning of the cortex. The findings are consistent with osteomalacia."

Diagnosis.—On the basis of the history, physical appearances and roentgenologic studies, a diagnosis of osteomalacia was made. On the advice of Dr. George R. Minot, the patient was transferred to a special ward for study and treatment.

METHOD OF STUDY

Changes in calcium metabolism occur so slowly that it was thought the patient would hardly survive a sufficient length of time to allow prolonged periods of clinical observation after offering various therapeutic agents. It was important, accordingly, to place the patient under strict metabolic observation so that the effect of treatment could be learned after comparatively few days of study. In addition to studies of the calcium, phosphorus and nitrogen metabolism, pertinent chemical examinations of blood and spinal fluid were made. X-ray pictures were taken of the entire skeleton of the patient under standard conditions, and complete measurements of the body were made at the beginning of treatment and at appropriate subsequent intervals. The first objective was to learn the endogenous calcium and phosphorus metabolism of the patient. As pointed out by Bauer, Albright and Aub,[41] the factors that influence calcium metabolism are many and must be kept constant if the comparative effects of different therapeutic agents are to be studied. We are indebted to Dr. Joseph C. Aub, Miss Constance Fulton and Miss Helen Heywood for their cooperation. Through the cooperation of Dr. Aub, it was possible to establish the proper routine and precautions as outlined in the following paragraphs.

41. Bauer, W.; Albright, F., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: II. The Calcium Excretions of Normal Individuals on a Low Calcium Diet, Also Data on a Case of Pregnancy, J. Clin. Investigation **7**:75, 1929.

The patient was placed in a room by herself, flat on her back on a Bradford frame. The patient and the nurse in charge were instructed that only the food given in the special diet was to be eaten by the patient, and that any food not eaten was to be weighed and noted by the dietitian. They were also informed that all excreta were to be saved for analysis.

Three diets, designated diet 1, diet 2 and diet 3, were used in the course of the metabolic studies. When it was desired to give more calcium or phosphorus than was provided for by the diet, calcium lactate and disodium acid phosphate were added to diet 2 or diet 3. Diet 1 (table 1), a neutral diet, low in calcium, and practically devoid of vitamins A and D, was given to the patient before medication was started, and at later times to learn the effect of treatment. Except for the low content of vitamin A and D, it was essentially like that given

TABLE 1.—*Diet 1. Low Vitamin, Low Calcium, Neutral Diet*

	Breakfast, Gm.	Dinner, Gm.	Supper, Gm.	Total Gm.	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calcium, Gm.	Phosphorus, Gm.	Excess Acid, Cc., Normal	Excess Base, Cc., Normal
Bacon	15	...	...	15	.....	3.45	10.05	0.004	0.014	1.78	.....
Bread, low in calcium	50	50	50	150	79.80	12.00	3.15	0.017	0.121	11.83	.....
Apple	100	...	100	200	27.00	0.60	1.00	0.020	0.036	.....	7.52
Steak	...	75	...	75	.....	15.95	6.00	0.006	0.129	9.00	.....
Potato	...	100	150	250	45.25	4.75	0.25	0.027	0.119	.....	15.85
Banana	...	100	...	100	21.00	1.10	0.60	0.007	0.042	.....	5.56
Honey	...	...	30	30	24.36	0.12	.....	0.001	0.005	.....	2.44
Chicken	...	...	40	40	.....	8.60	1.00	0.008	0.063	6.80	.....
Corn	...	100	...	100	19.00	2.80	1.20	0.005	0.062	1.70	.....
Sugar	20	10	10	40	40.00	.....	.....	.....	.....	.....	.....
Nut margarine	10	15	15	40	.....	.....	34.00	.....	.....	.....	.....
Coffee	200	...	...	200	.....	.....	.....	.....	.....	.....	.....
Tea	...	200	200	400	.....	.....	.....	.....	.....	.....	.....
Salt, 3 Gm.											
Total grams (calories 1,738)					256.41	49.37	57.25	0.095	0.591	31.71	31.37

by Bauer and Aub [42] in their studies of the calcium metabolism of a large number of normal persons. The results obtained in our patient could therefore be compared with those obtained by these authors in normal persons.[41] Diet 2 (table 2) was obtained by the addition of 250 cc. of boiled skimmed milk a day to diet 1. Finally, a diet rich in native vitamins, calcium and phosphorus and somewhat higher in calories was utilized, diet 3 (table 3). The plan of the diet and medication during the entire time of intensive study is given in table 4.

The patient was given the control diet (diet 1) for forty-eight hours before the collection of specimens for analysis was begun. She was then given 0.6 Gm. of carmine alum lake in a gelatine capsule at 8 a. m. before breakfast. The collection of the feces for the period started with the first appearance of the carmine in the stools. After three days, the patient was given 0.6 Gm. of charcoal at 8 a. m. before breakfast. The appearance of charcoal in the feces thus marked the end of the carmine period and the beginning of the next three-day

42. Bauer, W., and Aub, J. C.: Studies in Inorganic Salt Metabolism: I. The Ward Routine and Methods, J. Am. Dietet. A. **3**:106, 1927.

TABLE 2.—*Diet 2. Diet 1, Plus 250 Cc. Boiled Skimmed Milk Daily*

	Breakfast, Gm.	Dinner, Gm.	Supper, Gm.	Total Gm.	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calcium, Gm.	Phosphorus, Gm.
Skimmed milk	125	...	125	250	12.75	8.5	0.75	0.305	0.240
Salt, 3 Gm.									
Total grams, diet 1					256.41	49.37	57.25	0.095	0.591
Total grams, diet 2 (calories, 1,830)					269.16	57.87	58.00	0.400	0.831

TABLE 3.—*Diet 3. High Vitamin, High Calcium and Phosphorus*

	Breakfast, Gm.	Dinner, Gm.	Supper, Gm.	Total Gm.	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calcium, Gm.	Phosphorus, Gm.
Orange juice	75	...	...	75	8.1	.....	....	0.022	0.013
Eggs	50	...	50	100	....	13.40	10.5	0.067	0.180
Oatmeal	20	...	...	20	13.5	3.20	1.4	0.014	0.078
Bread	50	50	50	150	79.5	15.90	4.2	0.081	0.132
Butter	20	20	20	60	....	0.00	51.0	0.009	0.009
Milk (whole)	200	...	200	400	20.0	13.20	16.0	0.480	0.372
Cream, 20 per cent	50	...	...	50	2.3	1.30	9.3	0.043	0.034
Sugar	20	10	...	30	30.0	.....	....	.....	.....
Potato	...	100	...	100	20.0	1.90	0.1	0.011	0.048
Carrots	...	100	...	100	9.3	1.10	0.4	0.056	0.046
Steak	...	75	...	75	....	15.95	6.0	0.006	0.129
Ice cream	...	200	...	200	40.8	4.10	30.8	0.143	0.112
Lettuce	...	..	20	20	0.6	0.24	0.1	0.069	0.008
Olive oil	...	...	10	10	....	.....	10.0	.....	.....
Lemon juice	...	...	10	10	1.0	.....	....	0.002	0.001
Tomatoes (fresh)	...	...	100	100	4.0	1.20	0.2	0.007	0.055
Peaches (fresh)	...	...	100	100	9.4	0.70	0.1	0.016	0.024
Salt, 3 Gm.									
Total grams (total calories, 2,507)					238.5	72.79	140.2	0.967	1.241

TABLE 4.—*Plan of Diet and Medication*

Period	Diet	Medication
1, 2	1	Control periods, with no medication; low calcium and low vitamin
3, 4	2	No medication; sufficient calcium, low vitamin
5, 6	2	50 cc. cod liver oil daily, given with meals
7, 8	2	50 cc. cod liver oil, and 18 oscodal tablets daily, 6 at each meal
9, 10, 11, 12, 13	2	50 cc. cod liver oil, 18 oscodal tablets and ultraviolet irradiation* from a mercury quartz lamp, daily
14, 15	1	Control periods, with no medication; low calcium, low vitamin
16, 17, 18	2	50 cc. cod liver oil, 18 oscodal tablets, ultraviolet light, daily; in addition, 1.24 Gm. calcium as calcium lactate daily with meals
19, 20	1	Control periods with no medication; low calcium, low vitamin
21, 22, 23, 24	2	50 cc. cod liver oil, 18 oscodal tablets, ultraviolet light; in addition, 3 Gm. phosphorus, as disodium acid phosphate daily with meals
25, 26	1	Control periods with no medication; low calcium, low vitamin
27, 28, 29	2	50 cc. cod liver oil, 18 oscodal tablets, ultraviolet light; in addition, 1.24 Gm. calcium as calcium lactate and 3 Gm. phosphorus as disodium acid phosphate daily with meals
30, 31, 32, 33	3	Diet rich in native vitamins, calcium and phosphorus; cod liver oil, oscodal and ultraviolet light as above; calcium as calcium lactate and phosphorus as disodium acid phosphate added to make calcium and phosphorus intake same as in periods 27, 28 and 29

* The ultraviolet irradiation was given by means of an air-cooled mercury quartz lamp. At the beginning, the patient was exposed front and back for two minutes at a distance of 20 inches (50.8 cm.). This distance was decreased and the time of exposure increased in accordance with the reaction of the patient, so that at the end of the period of observation she was exposed for twenty minutes, at a distance of 6 inches (15.24 cm.).

stool period. The fecal periods were differentiated throughout the study by the alternate administration of carmine and charcoal in this manner. The three-day stool specimens were dried, weighed, ashed and extracted as described by Bauer and Aub.[42] The urine for the corresponding three-day periods was collected from 8 a. m. before breakfast on the first day, to 8 a. m. before breakfast on the fourth day; the patient always voiding in the morning before the beginning of the new period. A few cubic centimeters of chloroform and from 5 to 10 cc. of concentrated hydrochloric acid were added to the specimens of urine to preserve them and to keep the urine acid until the time of analysis, so that no ammonia would be lost. The total urinary output for each three-day period was well mixed, measured and examined by a routine urinalysis. An aliquot portion of the specimen was saved for chemical analysis.

The calcium contents of urine, feces, serum and spinal fluid were determined according to Fiske's method;[43] the phosphates of the urine, feces and serum by the method of Fiske and Subbarow,[44] and the urinary nitrogen by the method of Folin.[45] Blood hemoglobin was determined by the Newcomer method. The fecal nitrogen for each period was calculated as 10 per cent of the nitrogen intake for that period, and the total nitrogen output was estimated by adding the figures for the fecal and urinary nitrogen output.

The prolonged stay in bed and the low roughage in the diets caused the patient to become constipated, and either liquid petrolatum or cascara sagrada in tablet form was used as a cathartic. The calcium content of this medication, as given by Bauer and Aub,[42] as well as the calcium and phosphorus content of the cod liver oil concentrate, as determined by us, was added to the daily intake whenever these substances were given. Furthermore, the calcium content of the calcium lactate used in the diet was determined by analysis.

METABOLIC OBSERVATIONS

The results of period 1 (table 5), during which the patient received the low calcium, low vitamin, neutral diet (diet 1, table 1), demostrate strikingly the tendency of the patient to lose calcium and phosphorus. An average normal subject under a similar regimen has a negative calcium balance of 0.46 Gm. of calcium, or 6.7 mg. per kilogram, and is in approximate phosphorus equilibrium.[46] In periods 1 and 2, the patient showed an average loss of 1.79 Gm. of calcium, 45 mg. per kilogram, and 0.64 Gm. of phosphorus in three days. This is all the more significant since the patient received sufficient calories, as shown by the gain in body weight and the positive nitrogen balance. In periods 3 and 4, the calcium intake was quadrupled and the phosphorus intake greatly increased by adding 250 cc. of boiled skimmed

43. Fiske, C. H.: To be published.

44. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

45. Folin, O.: Kjeldahl's Method for the Determination of Nitrogen, Laboratory Manual of Biological Chemistry, New York, D. Appleton & Company, 1925, p. 59.

46. Bauer, W.: Personal communication to the authors.

milk to the diet (diet 2). Although the patient received amounts greatly in excess of the normal metabolic requirement, she continued in negative calcium and phosphorus balance. Fifty cubic centimeters of a physiologically tested preparation of cod liver oil, an amount much greater than that considered adequate by other investigators, was then added to her diet (periods 5 and 6), but no appreciable storage of calcium or phosphorus resulted. Since patients with pernicious anemia who take small amounts of liver (40 Gm. daily) usually experience no improvement in contrast with the rapid and striking improvement when adequate large amounts are taken,[47] it was thought that if our patient took much larger doses of cod liver oil it would be beneficial, although she had taken supposedly adequate amounts of cod liver oil both before and since entering the hospital. The properties of cod liver oil made this impossible, so a physiologically tested concentrate in tablet form was administered instead.[48] Eighteen tablets (the vitamin A equivalent of 180 cc. and the vitamin D equivalent of 38 cc. of cod liver oil, were given daily in addition to 50 cc. of cod liver oil. As shown in table 5, the patient was able for the first time to store appreciable amounts of calcium and phosphorus (periods 7 and 8). In periods 9 and 10 (table 5), ultraviolet light irradiation was added to the regimen. Conspicuous improvement in the patient's general condition was evident. The tenderness of the bones had disappeared, except over the pubis, and the patient felt stronger. The results were so gratifying, both clinically and from the standpoint of calcium and phosphorus retention, that the same therapeutic measures were continued for three more periods (11, 12 and 13) (table 5).

The patient was now definitely in positive calcium and phosphorus balance, but we believed that the retention might be further increased by giving larger amounts of the bone-forming elements. In order to learn the relative importance of calcium and phosphorus, each was increased separately. Later, both were given together in large amounts. In periods 16, 17 and 18, 1.24 Gm. of calcium in the form of chemically pure calcium lactate was added daily to the regimen of periods 9 to 13. Calcium lactate was used, because it is a neutral salt and is

47. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470 (Aug. 14) 1926.

48. Oscodal (Metz), a preparation of the nonsaponifiable fraction of cod liver oil, containing the antiophthalmic and antirachitic fat-soluble vitamins. It has 500 times the antiophthalmic (vitamin A) potency of cod liver oil when assayed by the method of the United States Pharmacopeia for cod liver oil, and its antirachitic (vitamin D) potency is such that 0.0002 Gm. of oscodal (equivalent in potency to 0.02 Gm. of the oil) per day will suffice to initiate recalcification in the leg bones of young albino rats in ten days. Each coated tablet contains 0.02 Gm. of oscodal.

TABLE 5.—*Calcium, Phosphorus and Nitrogen Metabolism per Three-Day Period*

Period	Weight of Patient, Kg.	Intake			Output									Metabolic Balances			Metabolic Balances per Kilogram			Comment
					Urine			Feces			Total									
		Calcium, Gm.	Phosphorus, Gm.	Nitrogen, Gm.	Calcium, Gm.	Phosphorus, Gm.	Nitrogen, Gm.	Calcium, Gm.	Phosphorus, Gm.	Nitrogen, Gm.	Calcium, Gm.	Phosphorus, Gm.	Nitrogen, Gm.	Calcium, Gm.	Phosphorus, Gm.	Nitrogen, Gm.	Calcium, Gm.	Phosphorus, Gm.	Nitrogen, Gm.	
1	39.2	0.33	1.83	23.70	0.80	1.32	19.32	1.45	1.21	2.37	2.25	2.53	21.69	−1.92	−0.70	+ 2.01	−0.049	−0.018	+0.051	Control diet 1, low in calcium, phosphorus and vitamins
2	40.4	0.32	1.83	23.70	0.88	1.57	20.81	1.10	0.83	2.37	1.98	2.40	23.18	−1.66	−0.57	+ 0.52	−0.041	−0.014	+0.013	
3	40.8	1.24	2.55	27.78	1.14	2.14	29.30	0.77	0.45	2.78	1.91	2.59	32.08	−0.64	−0.04	−4.30	−0.016	−0.001	−0.105	Diet 1 as in periods 1 and 2, plus 250 cc. boiled skimmed milk daily
4	40.7	1.24	2.55	27.78	0.99	1.06	22.59	1.12	0.66	2.78	2.11	2.32	25.35	−0.87	+0.23	+ 2.43	−0.021	+0.006	+0.060	
5	41.4	1.24	2.55	27.78	1.02	2.10	22.44	1.07	0.57	2.78	2.09	2.67	25.22	−0.85	−0.12	+ 2.56	−0.021	−0.003	+0.062	Same diet as in periods 3 and 4, plus 50 cc. cod liver oil daily
6	41.6	1.25	2.55	27.78	0.94	2.12	21.61	0.20	0.19	2.78	1.14	2.21	24.39	+0.11	+0.34	+ 3.39	+0.003	+0.008	+0.081	
7	41.6	2.00	2.55	27.78	0.90	1.65	20.46	0.74	0.58	2.78	1.64	2.23	23.24	+0.36	+0.32	+ 4.54	+0.009	+0.008	+0.109	Same diet and medication as in periods 5 and 6, plus 18 oscodal tablets daily
8	41.8	2.00	2.55	27.78	0.74	1.46	24.41	0.63	0.54	2.78	1.37	2.00	27.29	+0.63	+0.55	+ 0.49	+0.015	+0.013	+0.012	
9	42.5	2.00	2.55	27.78	0.63	1.21	21.42	0.31	0.32	2.78	0.94	1.53	24.20	+1.06	+1.02	+ 3.58	+0.025	+0.024	+0.084	Same diet and medication as in periods 7 and 8, plus daily treatment with ultraviolet light
10	42.1	2.00	2.55	27.78	0.75	1.38	21.03	0.14	0.12	2.78	0.89	1.50	23.81	+1.11	+1.05	+ 3.97	+0.026	+0.025	+0.094	
11	42.0	2.00	2.55	27.78	0.71	1.35	21.47	0.21	0.26	2.78	0.92	1.61	24.25	+1.08	+0.94	+ 3.53	+0.026	+0.022	+0.084	
12	42.0	2.00	2.55	27.78	0.46	1.23	19.68	0.08	0.08	2.78	0.54	1.31	22.46	+1.46	+1.24	+ 5.32	+0.035	+0.030	+0.127	
13	42.8	2.02	2.56	27.78	0.45	1.23	21.45	0.30	0.43	2.78	0.75	1.66	24.23	+1.25	+0.89	+ 3.55	+0.029	+0.021	+0.083	
14	42.5	0.35	1.83	23.70	0.39	1.39	18.51	0.13	0.19	2.37	0.52	1.58	20.88	−0.17	+0.25	+ 2.82	−0.004	+0.006	+0.066	Control diet 1, same as in periods 1 and 2
15	42.8	0.35	1.83	23.70	0.42	1.25	18.19	0.13	0.41	2.37	0.55	1.65	20.56	−0.20	+0.18	+ 3.14	−0.005	+0.004	+0.073	
16	43.0	5.74	2.55	27.78	0.64	0.62	12.88	1.24	0.36	2.78	1.88	0.98	15.66	+3.86	+1.57	+12.12	+0.090	+0.037	+0.282	Same diet and medication as in periods 9 to 13, plus calcium lactate
17	43.4	5.74	2.55	27.78	0.63	0.29	13.40	2.62	0.62	2.78	3.25	0.91	16.18	+2.49	+1.64	+11.60	+0.057	+0.038	+0.267	
18	43.4	5.75	2.55	27.78	0.49	0.39	15.61	0.93	0.26	2.78	1.42	0.65	18.39	+4.33	+1.90	+ 9.39	+0.100	+0.044	+0.219	
19	43.7	0.35	1.83	23.70	0.34	1.11	16.33	0.63	0.35	2.37	0.97	1.46	18.70	−0.62	+0.37	+ 5.00	−0.014	+0.009	+0.114	Control diet 1, same as in periods 1 and 2
20	43.2	0.36	1.83	23.70	0.22	1.05	17.55	0.12	0.36	2.37	0.34	1.41	19.92	+0.02	+0.42	+ 3.78	+0.001	+0.010	+0.087	
21	43.3	2.03	9.00	27.78	0.07	4.97	22.50	0.25	0.34	2.78	0.32	5.31	25.28	+1.97	+3.79	+ 2.50	+0.039	+0.088	+0.058	Same diet and medication as in periods 9 to 13, plus disodium acid phosphate
22	43.4	2.02	9.00	27.78	0.08	6.10	23.92	0.18	0.24	2.78	0.26	6.34	26.70	+1.76	+2.65	+ 1.08	+0.041	+0.061	+0.025	
23	43.5	2.03	9.00	27.78	0.09	6.94	30.69	0.29	0.31	2.78	0.38	7.25	33.47	+1.65	+1.75	+ 4.31	+0.038	+0.040	+0.099	
24	43.8	2.03	9.00	27.78	0.13	5.92	19.42	0.21	0.28	2.78	0.34	6.20	22.20	+1.69	+2.80	+ 5.58	+0.039	+0.064	+0.127	
25	43.5	0.36	1.83	23.70	0.28	1.88	17.07	0.24	0.38	2.37	0.52	2.26	19.44	−0.16	−0.43	+ 4.26	−0.004	−0.010	+0.098	Control diet 1, same as in periods 1 and 2
26	43.4	0.35	1.83	23.70	0.38	1.29	15.31	0.10	0.39	2.37	0.48	1.68	17.68	−0.13	+0.15	+ 6.02	−0.003	+0.003	+0.139	
27	44.4	5.75	9.00	27.78	0.23	4.33	18.28	1.24	0.75	2.78	1.47	5.08	21.06	+4.28	+3.92	+ 6.72	+0.096	+0.088	+0.151	Same diet and medication as in periods 9 to 13, plus calcium lactate and disodium acid phosphate
28	44.1	5.75	9.00	27.78	0.17	5.00	16.90	1.09	0.44	2.78	1.26	5.44	19.68	+4.49	+3.56	+ 8.10	+0.102	+0.081	+0.184	
29	44.9	5.75	9.00	27.78	0.22	5.19	18.62	0.76	0.33	2.78	0.98	5.52	21.40	+4.77	+3.48	+ 6.38	+0.106	+0.078	+0.142	
30*	45.5	5.78	9.00	34.95	0.22	5.26	21.12	1.71	0.86	3.50	1.93	6.11	24.62	+3.85	+2.89	+10.33	+0.085	+0.064	+0.227	Diet 3 plus cod liver oil, oscodal and ultraviolet light as above, also calcium lactate and disodium acid phosphate
31*	45.5	5.78	9.00	34.95	0.22	5.26	21.12	1.71	0.86	3.50	1.93	6.11	24.62	+3.85	+2.89	+10.33	+0.085	+0.064	+0.227	
32*	45.5	6.08	9.41	34.95	0.50	5.59	21.65	0.50	0.25	3.50	1.00	5.84	25.15	+5.08	+3.57	+ 9.80	+0.112	+0.078	+0.215	
33*	46.5	6.08	9.41	34.95	0.50	5.59	21.65	0.50	0.25	3.50	1.00	5.84	25.15	+5.08	+3.57	+ 9.80	+0.109	+0.077	+0.211	

* The results of periods 30 and 31 were obtained by dividing one six-day period by 2 for the purpose of comparison. The results of periods 32 and 33 were obtained similarly.

readily absorbed.[49] The daily amount was divided into three doses and given with the meals, so that the salt would be in the stomach and upper intestine when the environment was most acid and therefore most favorable for maximum absorption. As shown in table 5 and "block" G of figure 1, the retention of calcium was tripled and that of phosphorus significantly increased. Further analysis of these data will be given subsequently in this paper.

In order to demarcate the results, no medication was given in periods 19 and 20, and then 3 Gm. of phosphorus in the form of dis-

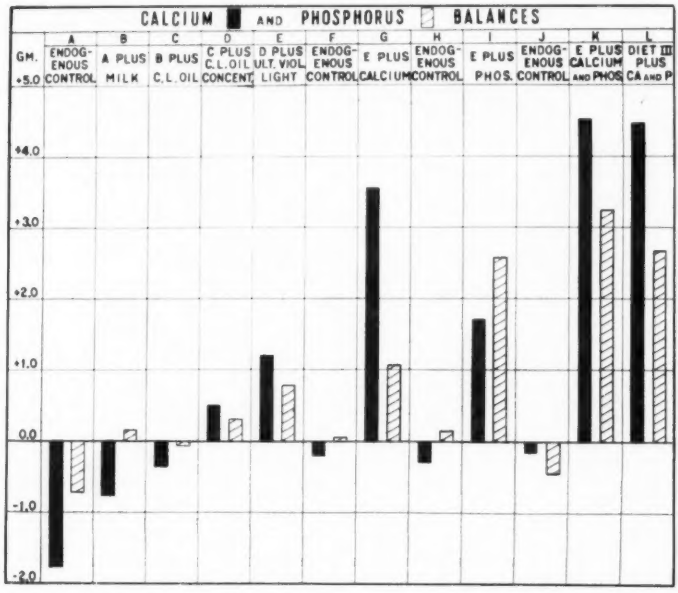

Fig. 1.—Calcium and phosphorus balances of patient with osteomalacia. The solid columns represent the actual calcium balance. The hatched columns represent the phosphorus balance obtained by subtracting the theoretical phosphorus combined with body protein from the actual phosphorus balance. Each section, lettered *A* to *L*, represents the average results of two or more consecutive three-day periods obtained on the regimen described briefly on the figure and in detail in the text.

odium acid phosphate was added daily to the diet and treatment as given in periods 9 to 13. Disodium acid phosphate was used because it is the most neutral of the sodium phosphate salts. It was given in three doses with meals, as was the calcium lactate.

49. Bauer, W., and Ropes, M. W.: The Effect of Calcium Lactate Ingestion on Serum Calcium, J. A. M. A. **87**:1902 (Dec. 4) 1926.

It was evident that the administration of phosphorus alone increased the retention of calcium just as the addition of calcium alone increased the retention of phosphorus.

These results clearly indicated the advisability of giving large amounts of both calcium and phosphorus, as well as large amounts of vitamins A and D, and this was, accordingly, done in periods 27, 28 and 29. As can be seen in table 5 and columns K in figure 1, the response of the patient was most gratifying.

In periods 30, 31, 32 and 33, part of the calcium and phosphorus which had previously been given as salts was given by means of foods (diet 3, table 3) rich in calcium and phosphorus. The fact that there was no significant change in the retention of the bone-forming elements indicates that administration of calcium and phosphorus in the form of salts is as efficacious as giving them in the form of native food content.

Phosphorus Metabolism.—In table 6, data are presented in a form that makes possible the comparison of the "theoretical" phosphorus balance with the actually determined phosphorus balance. The purpose of such a comparison is to discover to what degree retention and excretion of calcium and phosphorus denote alteration in the metabolism of bone. The term "theoretical phosphorus balance" refers to the phosphorus balance calculated from the nitrogen and calcium balances. The theoretical phosphorus retained or lost with nitrogen can be calculated with considerable confidence whereas the theoretical phosphorus retained or lost with calcium rests on the assumption that all the phosphorus not metabolized with nitrogen takes part in bone metabolism as calcium phosphate. It is consequently apparent that the extent to which the "theoretical phosphorus balance" and the actually determined phosphorus balance coincide provides a means of learning to what degree the phosphorus retained or excreted reflects changes in the metabolism of bone. The theoretical phosphorus retained or lost as protein has been calculated from the ratio of $\frac{\text{nitrogen}}{\text{phosphorus}} = \frac{17.4}{1}$ and the phosphorus retained or lost as bone from the ratio $\frac{\text{calcium}}{\text{phosphorus}} = \frac{2.3^{50}}{1}$. The method

50. Example:

Period 1. Calcium balance determined = 1.92 Gm.

Theoretical phosphorus balance calculated from calcium	$= \frac{1.92}{x} :: \frac{2.3}{1} = -0.86$ Gm.
Nitrogen balance determined	$= 2.01$ Gm.
Theoretical phosphorus balance	$= \frac{2.01}{x} :: \frac{17.4}{1} = +0.12$ Gm.
Total theoretical phosphorus balance	$= -0.86 + 0.12 = -0.74$ Gm.

employed here is that used by Albright, Bauer, Ropes and Aub.[46] The results show that actual and calculated phosphorus balances agree closely during both the period of negative and that of positive calcium balances. This demonstrates that measurement of the calcium and phos-

TABLE 6.—*Comparison of Actual and Calculated Phosphorus Balances*

	Phosphorus Balances					
Period	Theoretical, Calculated from Calcium Balance, Gm.	Theoretical, Calculated from Nitrogen Balance, Gm.	Total, Theoretical, Gm.	Actual, Gm.	Difference, Actual Minus Calculated, Gm.	Phosphorus Intake, Gm.
1	−0.86	+0.12	−0.74	−0.70	+0.04	1.83
2	−0.75	+0.03	−0.72	−0.57	+0.15	1.83
3	−0.29	−0.25	−0.54	−0.04	+0.50	2.55
4	−0.39	+0.14	−0.25	+0.23	+0.48	2.55
5	−0.38	+0.15	−0.23	−0.12	+0.11	2.55
6	+0.05	+0.20	+0.25	+0.34	+0.09	2.55
7	+0.16	+0.26	+0.42	+0.32	−0.10	2.55
8	+0.28	+0.03	+0.31	+0.55	+0.24	2.55
9	+0.48	+0.21	+0.69	+1.02	+0.33	2.55
10	+0.50	+0.23	+0.73	+1.05	+0.32	2.55
11	+0.49	+0.20	+0.69	+0.94	+0.25	2.55
12	+0.66	+0.31	+0.97	+1.24	+0.27	2.55
13	+0.56	+0.20	+0.76	+0.89	+0.13	2.55
14	−0.08	+0.16	+0.08	+0.25	+0.17	1.83
15	−0.09	+0.18	+0.09	+0.18	+0.09	1.83
16	+1.73	+0.70	+2.43	+1.57	−0.86	2.55
17	+1.11	+0.67	+1.78	+1.64	−0.14	2.55
18	+1.94	+0.54	+2.48	+1.90	−0.58	2.55
19	−0.28	+0.29	+0.01	+0.37	+0.36	1.83
20	+0.01	+0.22	+0.23	+0.42	+0.19	1.83
21	+0.75	+0.14	+0.89	+3.79	+2.90	9.00
22	+0.79	+0.06	+0.85	+2.66	+1.81	9.00
23	+0.73	+0.25	+0.98	+1.75	+0.77	9.00
24	+0.76	+0.32	+1.08	+2.80	+1.72	9.00
25	−0.07	+0.25	+0.18	−0.43	−0.61	1.83
26	−0.06	+0.35	+0.29	+0.15	−0.14	1.83
27	+1.92	+0.39	+2.31	+3.92	+1.61	9.00
28	+2.01	+0.47	+2.48	+3.56	+1.08	9.00
29	+2.14	+0.37	+2.51	+3.48	+0.97	9.00
30*	+1.72	+0.59	+2.31	+2.89	+0.58	9.00
31*	+1.72	+0.59	+2.31	+2.89	+0.58	9.00
32*	+2.28	+0.56	+2.84	+3.57	+0.73	9.41
33*	+2.28	+0.56	+2.84	+3.57	+0.73	9.41

* The results of periods 30 and 31 were obtained by dividing one six-day period by 2 for the purpose of comparison. The results of periods 32 and 33 were obtained similarly.

phorus balances as accomplished in this study affords a direct approach to the study of the metabolism of bone.

In view of the close correspondence in most of the periods, the occasional discrepancies are of considerable interest. In periods 16, 17 and 18 (table 6), in which the calcium intake was increased without a corresponding increase in phosphorus, more phosphorus was excreted than theoretically expected. It may seem curious that all of the small

amount of phosphorus available in the diet was not entirely utilized in conjunction with calcium. The actual total phosphorus output in these periods (average 0.28 Gm. per diem) is the lowest that occurred during the study of this case and is as low as any we have been able to find recorded in the literature. It may well be the result of the endogenous metabolism of protein and of bone, and as such it would not be available in forming new bone. According to this concept, all the available phosphorus was used to form calcium phosphate and the additional calcium retained was possibly deposited as calcium carbonate in excess of the normal ratio.

In periods 21 to 24 (table 6) inclusive, the converse of this situation was established, for, instead of increasing the calcium separately, the phosphorus was increased without a corresponding addition of calcium. On a phosphorus intake of 9 Gm. for a three-day period, an average of 1.8 Gm. of phosphorus was retained in excess of that theoretically expected. To be sure, the increased amounts used lead to an increase in the absolute error of measurement but not to a degree sufficient to account for the results. It might be expected that, with the deposition of this large amount of phosphorus, all available calcium would have been utilized. The explanation, again, may lie in the fact that the calcium excreted was not available inasmuch as it represented the endogenous calcium metabolism of bone. This explanation is supported by the low total calcium output (average 0.11 Gm. per diem) in these periods, the output being lower than in any other periods in our study or in any others reported in the literature. The form in which the phosphorus was utilized cannot be stated, although it is conceivable that phosphate salts of other cations such as magnesium may have been deposited.

Observations on the Blood and Spinal Fluid.—All observations on the blood and spinal fluid were made on specimens drawn after a fast of from fourteen to sixteen hours' duration. The calcium and inorganic phosphorus contents of the serum and the concentration of the peripheral hemoglobin and red blood cells, which were determined at frequent intervals during ten months of observation, are given in table 7. The calcium content of the serum was 10.7 mg. per hundred cubic centimeters on June 5, 1928, during period 1, and remained always within the accepted limits of normal for the entire time of observation. The inorganic phosphorus content was 2.24 mg. per hundred cubic centimeters on June 5, 1928, before treatment was started, and remained definitely below normal throughout the course of treatment. The two highest figures, 2.64 and 2.94 mg. per hundred cubic centimeters, were obtained on Aug. 10, 1928, and on Nov. 27, 1928, respectively, during periods of high phosphate medication. There was

a slight secondary anemia at the beginning of treatment, but this vanished by the time of the last observations. The white blood cell count was repeated at frequent intervals during these months and ranged from 4,000 to 7,000 per cubic millimeter. The carbon dioxide combining power of the serum was 56.6 per cent by volume; the nonprotein nitrogen of the blood was 26 mg., and the blood sugar 94 mg. per hundred cubic centimeters before treatment. The plasma fibrinogen by the method of Wu [51] was 0.37 per cent in the first month of treatment, and the sedimentation rate determined and transposed to a reference

TABLE 7.—*Studies of the Blood*

Date, 1928-1929	Serum Calcium, Mg. per 100 Cc.	Serum Inorganic Phosphorus, Mg. per 100 Cc.	Hemoglobin, per Cent	Red Blood Cells, Millions per C.Mm.
May 23	....	....	..	3.5
May 24	10.8*	....	..	...
May 25	11.2*	....	..	...
June 5	10.7	2.24	62	...
June 12	10.4	2.24	62	4.2
June 20	10.5	2.28	63	...
June 29	....	2.16	62	...
July 3	10.3	2.14	..	...
July 11	11.0	2.32	65	4.1
July 20	10.3	2.36	..	...
July 26	10.2	2.38	63	...
August 10	10.6	2.64	72	...
August 14	....	2.56	..	...
September 8	11.0	2.40	68	...
October 19	10.1	2.30	..	...
November 21	10.1	2.40	75†	4.6
November 27	10.4	2.94	75†	4.6
January 2	10.9	2.21	85†	4.8
March 1	11.1	2.19	85†	4.3
March 22	10.9	2.59	..	...

* These determinations of calcium were made by the Clarke modification of the Kramer-Tisdall method (J. Biol. Chem. **63**: 461, 1925).

† These estimations of hemoglobin were made by the Talquist method; the others, by the Newcomer method.

hematocrit according to the method of Rourke and Ernstene [52] was 0.61 mm. per minute. Both these figures are well above the upper limits found for healthy persons. Repetition of these determinations five months after treatment showed the normal value of 0.28 per cent for fibrin and a sedimentation rate of 0.1 mm. per minute. The abnormally high values of these measurements before treatment may have been associated with the pathologic changes in the bone, while the normal values

51. Wu, H.: A New Colorimetric Method for the Determination of Plasma Proteins, J. Biol. Chem. **51**:33, 1922.

52. Rourke, M. D., and Ernstene, A. C.: To be published.

after treatment may have been due to the arrest of the process. The Wassermann and Kahn tests of the blood were negative on repeated examination during the year of observation.

Lumbar puncture was not done until March 1, 1929, ten months after treatment had started, because of the tenderness and deformity of the spine before this time. The fluid was clear, and the pressure normal. The Wassermann reaction and the colloidal gold curve were negative. The calcium content was 6.3 mg. per hundred cubic centimeters, and the calcium content of blood serum taken simultaneously was 11.1 mg. per hundred cubic centimeters.

The inorganic phosphorus content of the spinal fluid was 0.84 mg. and of the serum 2.20 mg. per hundred cubic centimeters. According to Fremont-Smith,[53] the calcium content of the spinal fluid is normal, but the phosphorus concentration is strikingly low. The normal proportionality of $\frac{\text{spinal fluid calcium}}{\text{serum calcium}}$ and of $\frac{\text{spinal fluid phosphorus}}{\text{serum phosphorus}}$ was present in this patient in spite of the extremely low phosphorus values.

ROENTGEN OBSERVATIONS

Figures 2, 3 and 4 show the appearance of the skull, pelvis and hands compared with a normal hand. The extreme degree of decalcification is evident. Figures 5, 6 and 7 show the appearance of the same parts of the body on Sept. 12, 1928, approximately three months after the institution of treatment. The roentgen report at that time was: "The thinning and atrophy of the bones is definitely less marked than when the patient was last seen. The bones are, however, somewhat less dense than normal even at this time."

By the time the last metabolic observations were concluded, three months from the beginning of the studies, the patient felt much stronger, the exquisite tenderness of the ribs and other bones had disappeared, and anemia was less marked. The patient then weighed 103 pounds (46.7 Kg.) in contrast with 86½ pounds (39.2 Kg.) before treatment. Proper orthopedic measures were instituted owing to the cooperation of Dr. Joseph H. Shortell of the Boston City Hospital and later of Dr. Mark Rogers of the Beth Israel Hospital. The effects of the dietary and orthopedic treatment were so striking that the patient was able to be up and about and left the hospital two weeks after the final metabolic studies had been completed. The beneficial dietary and orthopedic procedures were continued at home. During the past year, the patient has felt entirely well and has done all the housework for her family of four. She comes to the hospital twice weekly for ultraviolet irradiation. The skeletal measurements of the patient before, during

53. Fremont-Smith, F.: Personal communication to the authors.

Fig. 2.—Roentgenogram of the skull before treatment.

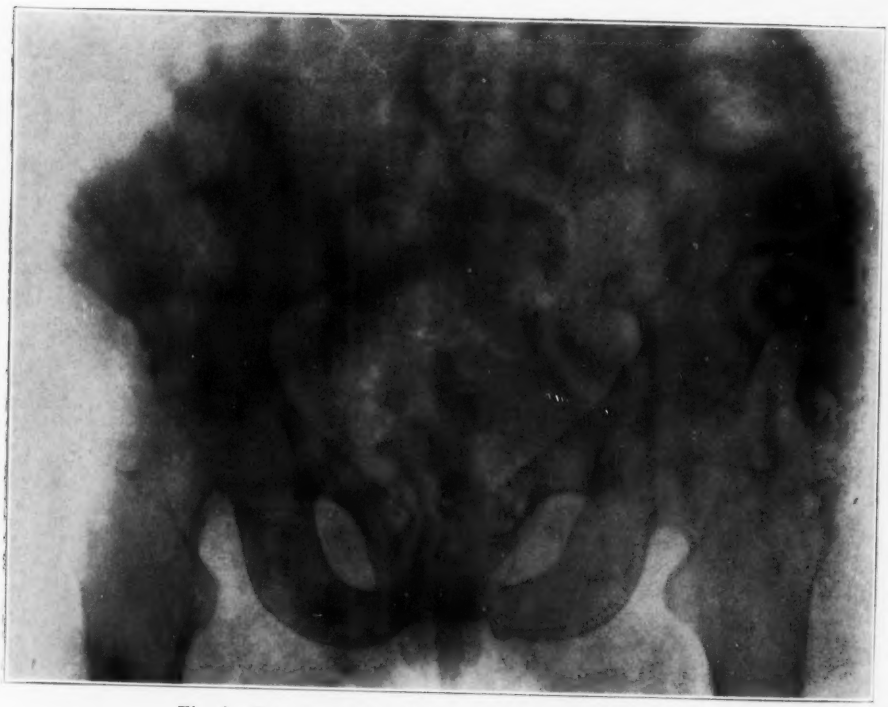

Fig. 3.—Roentgenogram of the pelvis before treatment.

Fig. 4.—Roentgenogram of the hands, compared with a normal hand, before treatment.

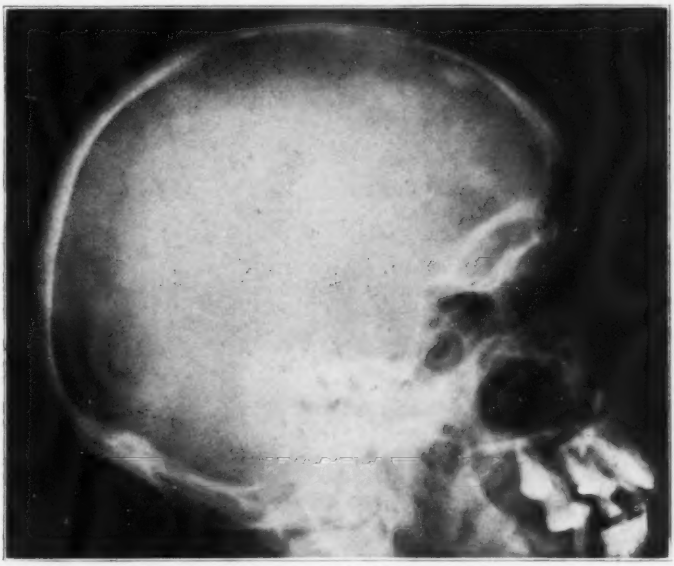

Fig. 5.—Roentgenogram of the skull after treatment.

Fig. 6.—Roentgenogram of the pelvis after treatment.

Fig. 7.—Roentgenogram of the hands, compared with a normal hand, after treatment.

and after treatment are given in table 8. Of particular interest is her increase in height due partially to the application of proper braces and the correction of curvatures while the bones were still soft.

COMMENT

The patient aroused considerable clinical interest because of the extreme rarity of the condition in the United States. According to

TABLE 8.—*Measurements of Patient*

Parts of Body	June 1, 1928	Sept. 14, 1928	June 1, 1929
Head			
Diameters, Cm.			
Biparietal	11.0	14.0	13.5
Front of ears, 1 cm., and below parietal eminence, 4 cm.	11.5	14.5	14.5
Occipitofrontal	13.0	18.0	17.5
Root of nose to base of occiput	14.5	16.0	15.5
Between malars	9.0	12.0	12.0
Root of nose to tip of chin	8.5	12.0	11.5
Circumferences, Cm.			
Parietal	48.75	51.0	51.0
Just above ears	51.25	52.5	52.0
Through root of nose and occipital protuberance	50.6	51.0	52.0
Neck circumference, Cm.	28.75	29.0	30.0
Chest at nipple line, circumference, Cm.	71.25	88.0	87.0
Abdomen at umbilicus, circumference, Cm.	72.5	90.0	82.0
Pelvis			
Circumference, Cm.	77.5	89.0	86.0
Diameters, Cm.			
Interspinous	20.0	22.0	21.0
Intercristal	26.0	29.0	27.0
External conjugate	17.0	21.0	20.0
External oblique	R 22.0	22.0	22.0
	L 20.0	22.0	21.0
Extremities, length, Cm.			
Upper limb	R 65.0	69.0	68.0
	L 65.0	69.0	68.0
Upper arm	R 26.25	28.0	30.0
	L 26.25	28.0	30.0
Forearm	R 24.1	24.0	24.0
	L 23.1	24.0	24.0
Hand	R 15.6	17.0	14.0
	L 15.6	17.0	14.0
Lower limb	R 80.0	83.0	82.0
	L 80.0	83.0	82.0
Thigh	R 38.7	40.0	38.0
	L 38.7	40.0	38.0
Leg below knee	R 35.0	37.5	36.0
	L 35.0	37.5	36.0
Foot	R 20.6	22.0	20.0
	L 20.6	22.0	20.0
Body			
Total height, Cm.	148.0	151.0	158.0
Sitting height, Cm.	70.6	71.0	76.0

Locke,[54] the disease is among the rarest of the bone diseases in this country. In 216,799 admissions to the Boston City Hospital during the years from 1915 to 1928, there were only 2 other instances of the disease. Although the incidence of osteomalacia is higher in women who have had repeated pregnancies than in other persons, it is excep-

54. Locke, E. A.: Osteomalacia, in Oxford Medicine, New York, Oxford University Press, 1927, vol. 4, p. 462.

tional for the disease to continue to progress steadily for several years following the termination of pregnancy.

The occurrence of such an extreme manifestation of the disease raised the expectation that endocrine or dietary factors might be revealed to account for the condition. No dietary deficiency or endocrine abnormality appeared obvious. On the contrary, in view of the remarkable effects following administration of 100 Gm. of cod liver oil reported by certain foreign observers, it was of particular interest that the patient's condition had become steadily worse in spite of 2 tablespoonfuls of unrefined, fresh cod liver oil every other day. The only evidence of endocrine imbalance was afforded by the history of the pseudocyesis, but the reliability of the patient proved too uncertain to allow emphasis on this phenomenon. Clinical and experimental evidence indicates that the pituitary gland and the ovaries are closely interrelated, and it may not be without significance that two instances of pseudocyesis which have recently come to the notice of one of us should have occurred in a patient with osteomalacia and in a patient with diabetes insipidus.

The disease as manifested in our patient corresponded with the advanced form observed in other parts of the world, in that the ribs, pelvis and long bones were particularly affected. The excruciating nerve root pain, the blue sclerotics, the anemia, the conspicuous muscular weakness, the "waddle gait" and the evidences of decalcification of the bone likewise were manifestations of the disease similar to those observed elsewhere. Unlike the patients studied by Miles and Feng [38] in China, however, the level of the serum calcium was normal and that of the serum phosphorus was definitely lowered. The relation of the condition in our patient to "hunger osteomalacia" is uncertain, for the Viennese observers [35] noted an absence of deformities of bone and a disappearance of symptoms on administration of moderate doses of cod liver oil. While "hunger osteomalacia" may represent an early stage of the advanced form, nevertheless it seems that our patient should have been alleviated by the fresh, unrefined cod liver oil which she had taken for some months.

Whether the fundamental metabolic fault of the patient has been altered cannot be stated. While the patient excreted far less calcium and phosphorus in control periods 14, 15, 19, 20, 25 and 26 (table 6) than in periods 1 and 2 before treatment was instituted, this may have been due to a persistence of action of the immediately preceding therapeutic measures rather than to any fundamental change in metabolism. The fact that the abnormally low level of serum phosphorus has not changed during the year in spite of treatment and clinical improvement indicates that the fundamental metabolic fault has not been altered.

In the course of our study of this patient, we failed to discover any evidence of endocrine abnormality. Recently, Barr, Bulger and

Dixon,[11] and Wilder[12] reported cases showing undoubted evidences of hyperparathyroidism with osteitis fibrosa cystica. Their cases resemble that of our patient in that softening of the bone with decalcification was present and in that the condition was benefited by a diet high in vitamin D and daily treatment with ultraviolet light. In contrast with our patient, however, their patients showed an elevated level of the serum calcium, multiple benign giant cell tumors of the bones, tumors of the parathyroid glands and bone cysts. These facts, together with the remarkable manner in which our patient recovered her strength and maintained it on a diet high in vitamins A and D and ultraviolet light treatment and without surgical excision of the parathyroid glands, indicate that the condition in our patient was not due to a primary disorder of the parathyroid glands, and differs fundamentally from the cases of osteitis fibrosa cystica reported.

Why our patient required more vitamin substances than other, normal persons is obscure. Certain features strongly suggest, however, that osteomalacia, as observed by us, is a form of adult rickets.

Clinical Similarities Between Osteomalacia and Rickets.—Clinically, the same bones as in rickets were most prominently affected. The roentgen appearance of the epiphyses was likewise strikingly similar to that observed in adult rickets by Hutchison and Stapleton.[33] The softening of the bones appeared at the time of year in which the highest percentage of the manifestations of rickets occurs.[55]

Metabolic Similarities.—It is now established that there are four factors, any one of which plays an important part in the production of rickets: calcium, phosphorus, vitamin D and ultraviolet radiation.[56] Orr, Holt, Wilkins and Boone[56] stated that cod liver oil and ultraviolet light irradiation facilitate absorption of calcium and phosphorus from the intestine in rickets. In this connection, it is of interest that the fecal calcium and phosphorus output in our patient became conspicuously less after the administration of cod liver oil concentrate and ultraviolet light. Whether this was due to increased absorption or to decreased excretion of calcium into the bowel, or to both, cannot be stated. In any event, these observations are in accord with those in rickets. Cod liver oil contains vitamins A and D. Irradiation with ultraviolet light may ameliorate conditions due to vitamin D deficiency, but cannot act as a substitute for this factor when it is completely absent from the diet. When given with vitamin D, however, it greatly increases

55. Lawrens, H.: Physiologic Effects of Radiation, Physiol. Rev. **8**:1, 1928.

56. Orr, W. J.; Holt, L. E.; Wilkins, L., and Boone, F. H.: The Calcium and Phosphorus Metabolism in Rickets, with Special Reference to Ultraviolet Ray Therapy, Am. J. Dis. Child. **26**:362 (Oct.) 1923.

the deposition of calcium. The fact that the retention of calcium became marked when ultraviolet light was given to our patient, in addition to cod liver oil concentrate, calcium and phosphorus, indicates again the similarity between our patient's osteomalacia and rickets. It is of interest in this connection that Steenbock [57] established the identity of irradiated ergosterol and vitamin D, and Goldstein [39] and Starlinger [40] reported clinical improvement in osteomalacia following the administration of irradiated ergosterol.

Blood Similarities.—The blood calcium of our patient was normal, while the blood phosphorus was definitely and persistently lowered, observations which again are in accord with observations in cases of rickets.[58]

Because of these clinical, metabolic, x-ray picture and blood similarities, and because of the striking retention of calcium and phosphorus when ultraviolet light and vitamins A and D were given, we believe that osteomalacia, as manifested by this patient, is a form of rickets that occurs in adults.

SUMMARY AND CONCLUSIONS

1. A case of advanced osteomalacia occurring in a young American woman is reported.

2. The endogenous calcium, phosphorus and nitrogen metabolism were studied under rigidly controlled conditions, and the effect of various therapeutic agents was observed over a period of more than one year.

3. Whereas an average normal person receiving a diet low in calcium, low in phosphorus and low in vitamin has a negative calcium balance of 6.7 mg. per kilogram, the patient studied showed an average loss of 45 mg. of calcium per kilogram of body weight. The negative calcium balance persisted even when the patient received an amount of calcium greatly in excess of the normal metabolic requirements.

4. Previous to the time the studies were commenced, the patient's condition had become progressively worse in spite of her taking 30 cc. of fresh, unrefined cod liver oil on alternate days for six months before admission. The first therapeutic agent utilized during the study was 50 cc. daily of a physiologically tested preparation of cod liver oil.

57. Steenbock, H., and Nelson, M. T.: XIX. The Induction of Calcifying Properties in a Rickets-Producing Ration by Radiant Energy, J. Biol. Chem. **62**: 209, 1924.

58. Anderson, G. H.: The Calcium and Phosphorus Content of the Blood in Normal and Rachitic Children: I. Calcium, Brit. J. Child. Dis. **21**:33, 1924; II. Phosphorus, ibid. **21**:107, 1924.

This failed to cause an appreciable storage of calcium, although the amount given was much greater than that found effective in osteomalacia by other investigators.

5. When, however, a cod liver oil concentrate was fed so that the patient received very large amounts of vitamins A and D, improvement in the patient's condition became evident. This became even more conspicuous when ultraviolet light irradiation was added. Considerable amounts of calcium and phosphorus were deposited in the bones, as shown by the results of metabolism studies, as well as by the increased density of the bones according to the x-ray pictures. The tenderness of the bones and the anemia disappeared, and the patient showed striking clinical improvement under this treatment.

6. The storage of calcium and phosphorus was greatly increased by the addition of large amounts of these elements in the form of calcium lactate and disodium acid phosphate. When a preponderance of calcium was added to the diet, phosphorus, as well as calcium, was deposited in increased amounts. The converse occurred when a preponderance of phosphorus was added to the diet. Maximum retention occurred, however, when the increased amounts of both elements were fed simultaneously.

7. Observations on the phosphorus metabolism indicate that the calcium retained was deposited as bone.

8. The clinical, metabolic, blood and roentgen observations, together with the striking retention of calcium and phosphorus when ultraviolet light and vitamins A and D were given, lead us to believe that osteomalacia as manifested by this patient is a form of adult rickets.

LYMPHOSARCOMA

WITH INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM *

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The brain and spinal cord are rarely the seat of direct invasion by lymphosarcomatous masses. Occasionally the structures about the central nervous system, such as the bones of the skull or the vertebrae, may show the presence of lymphosarcomatous nodules. Ewing [1] mentioned that with involvement of the cervical lymph nodes, the lesion may invade the wall of the pharynx, the tonsils and the base of the skull. Murchison,[2] in 1870, described a case in which a small growth existed in the dura mater above the foramen magnum, and Mosler,[3] in 1872, found in another case some small lymphoid tumors above the optic foramen. Roncalli,[4] in 1894, reported a case of lymphosarcoma with erosion of the base and dura. Guillain, Alajouanine and Perisson [5] claimed to be the first to report lymphosarcomatous involvement of the spinal cord. The extramedullary masses found at operation compressed the cord, causing a complete paraplegia. Elsberg,[6] in his book on tumors of the spinal cord did not mention any cases of compression of the cord due to these types of tumors. The scarcity of cases showing secondary involvement of the nervous structure, especially the report of only one case in the literature in which the spinal cord was compressed, is the reason for this presentation.

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* From the Neuropathological Laboratory, Montefiore Hospital, New York.

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2. Murchison, C.: Case of Lymphadenoma of the Lymphatic System, Spleen, Lungs, Liver, Heart, Diaphragm, Dura Mater, etc., Tr. Path. Soc. Lond. **21**:372, 1870.

3. Mosler, F.: Zur Histologie der Leukämie, Virchows Arch. f. path. Anat. **56**:14, 1872.

4. Roncalli, F.: Sarkom des Nasenrachenraumes, Jahrb. u. d. Chir. Abt. d. Spit. zu Basel, 1892, p. 19.

5. Guillain, Alajouanine and Perisson: Lymphosarcome extradural metastatique, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1057, 1925.

6. Elsberg, C.: Tumor of the Spinal Cord, New York, Paul B. Hoeber, Inc., 1925.

MATERIAL

Since 1922, twenty-six cases of lymphosarcoma were admitted to the Montefiore Hospital. Of these, seven presented neurologic signs, four of which were verified post mortem. Three of the cases presented signs of compression of the spinal cord, the remaining one showing involvement of the brain (table).

Cases of Lymphosarcoma with Involvement of the Nervous System

No	Sex*	Age	Duration of Illness	Onset		Clinical Diagnosis	Neurologic Diagnosis	Response to Deep Roentgen or Radium Treatment	Observations from Autopsy or Biopsy
				General Symptoms	Neurologic Signs				
1	♀	61	1 year 9 months	Gradual	Gradual	Lymphosarcoma	Extramedullary neoplasm	Improvement early without any response later (deep roentgen only)	Generalized lymphosarcomatosis with metastasis to dura
2	♂	40	1½ years	Sudden	Sudden	Lymphosarcoma; hydrothorax	Herpes zoster	Relief early; no response later (deep roentgen only)	Generalized lymphosarcoma; pleural effusion; extramedullary neoplasm
3	♂	32	9 months	Sudden	Sudden	Neoplasm of right lung	Metastasis to cord; possibility of subacute combined degeneration	Early improvement; no response later	Lymphosarcoma of right lung; empyema; extramedullary deposits
4	♂	45	1 year 11 months	Sudden	Sudden	Generalized lymphosarcoma	Generalized lymphosarcoma with involvement of the meninges at the base of the skull	Temporary remission of glandular enlargement early; pain in this case was not relieved	Generalized lymphosarcomatosis with invasion of middle and posterior fossae
5	♂	64	Discharged in 1922 and not heard from since	Sudden	Sudden	Lymphosarcoma	Lymphosarcoma with invasion of posterior cranial fossa	Early improvement with recession of enlargements and symptoms	Biopsy; lymphosarcoma
6	♂	37	7 months	Sudden	Gradual	Lymphosarcoma of left lung with metastasis	Lymphosarcoma with metastasis to vertebral column	Improvement early with no response later (roentgen and radium)	Pleural exudate containing tumor cells
7	♀	38	8 months	Sudden	Gradual	Lymphosarcoma of neck	Left peripheral facial palsy	No benefit from either roentgen or radium (roentgen and radium)	Biopsy; lymphosarcoma

* In this column, ♂ indicates male; ♀ female.

REPORT OF CASES

Group 1: Cases Showing Involvement of the Central Nervous System Which Came to Autopsy (table).—Case 1.—M. H., a woman, aged 61, entered the Montefiore Hospital on Feb. 21, 1924. Early in January, 1923, she had complained of a heavy feeling in the abdomen and a dull aching pain in the lower left side of the chest, later followed by attacks of sharp pains in the hypogas-

trium and the back. In July, she had noticed a lump on the right hip followed by a sensation of tingling and numbness of the soles gradually ascending to the middle of the thighs and accompanied by weakness of the extremities. The past history was unimportant.

Examination.—Physical examination showed the patient poorly nourished and developed. There was lagging of the right side of the chest with dulness on percussion and tubular breathing posteriorly. The lymph glands of the neck and axillae were not palpable. Several hard masses, with rounded edges, were felt in the right iliac region and in the groins.

On July 31, 1924, the neurologic examination showed marked nutritional wasting of the musculature. The deep tendon reflexes were active and equal. There were a bilateral Babinski sign and all confirmatory reactions. The sensory examination showed diminished vibratory sense, a definite loss of the sense of muscle position and hypesthesia and hypalgesia from the tenth dorsal segment down. There was a belt of hyperalgesia between the eighth and tenth dorsal vertebrae. The abdominal reflexes were moderately active. Pain on pressure was elicited over the vertebrae between the seventh and eighth dorsal segments.

Laboratory Observations.—Roentgen examination of the chest revealed a pleural effusion at the right base extending to the sixth rib. The superior mediastinum on the left side showed an infiltrating mass suggestive of neoplasm. The blood count showed: hemoglobin, 70 per cent; red blood cells, 3,970,000; white blood cells, 11,200. The differential count was normal.

Course.—The patient received seventeen deep roentgen treatments of the various involved regions. With the exception of some improvement in the motion of the lower extremities and some recession of the glandular enlargement at the beginning of the administration of the rays, the symptoms became worse, and the patient died on October 23.

The anatomic diagnosis was generalized lymphosarcomatosis, right hydrothorax and fibrinous pericarditis.

Autopsy.—Gross Examination: The cervical lymph glands were slightly enlarged. A large mass in the anterior mediastinum was adherent to the sternum which in turn was replaced by tumor tissue. The bronchial root glands, those about the celiac axis and the chain along the vertebral column extending into the pelvis were all enlarged. The spinal cord showed a thickened dura with a flat friable tumor mass limited to the posterior surface of the lower dorsal and upper lumbar segments. When the cord was sectioned at this level, a translucency of the posterior and lateral columns was observed.

Microscopic Examination of the Tumor: The tumor consisted of fairly uniform, small, polygonal, irregular nuclei. In some instances, the latter were pale-staining and occasionally multilobulated, with a moderate number showing mitosis. Rarely was a syncytial cell found. In places the cells were small and round resembling lymphocytes. The masses of cells were separated by a delicate stroma.

At the ninth dorsal segment of the spinal cord, there was a demyelination of the posterior columns and the crossed pyramidal tracts. There was an ascending degeneration of the posterior columns above that level (fig. 1 *A*) and a descending degeneration of the crossed pyramidal tracts below the ninth dorsal segment (fig. 1 *B*).

The interesting features of this case were the rapid progression of the symptoms, the neurologic being the most outstanding; the absence of any enlargement of the glands of the neck until late in the disease, and

Fig. 1.—*A*, midthoracic region showing ascending demyelination of posterior columns (*d.p.c.*). *B*, lumbar region, showing descending demyelination of posterior pyramidal tracts (*d.c.p.tr.*). Weil stain; × 30.

the occasional return in the power of the lower extremities owing to the recession of the tumor following deep roentgen therapy.

CASE 2.—D. S., a man, aged 40, a dress operator, was admitted to the Montefiore Hospital on Sept. 25, 1924. In April, 1924, he developed a dry cough, became dyspneic and felt somewhat weak. A diagnosis of pleural effusion was made. Pleural fluid was aspirated from his chest, following which he lost 16 pounds (7.3 Kg.) and developed a sharp pain in the lower right side of the chest. Fluid was repeatedly aspirated from the pleural cavity. A biopsy on a gland from the neck proved to be a lymphosarcoma. He received deep roentgen therapy which caused a disappearance of all the glands and improvement in his general condition, so that he was able to get about. In July, he became bedridden, his glands enlarged, he was markedly dyspneic, his feet were edematous and he developed a rash over the body and pains on both sides of the chest.

The past history was unimportant.

Examination.—Physical examination showed a bedridden and dyspneic patient with the knees flexed on the abdomen. The glands of the neck were enlarged bilaterally. The tonsils were extremely enlarged, red and cryptic and almost met in the midline. Enlarged, discrete, rubbery glands were found on either side of the face. The chest was asymmetrical, the left side being fuller than the right and expanded poorly. There were diminished fremitus on the left side, dulness on percussion from the third rib down anteriorly and posteriorly and diminished breathing on both sides, more marked on the left. A systolic murmur throughout the precordium, with the greatest intensity in the apex, was transmitted to the axilla. The liver was palpable on the right side four fingerbreadths below the costal margin. The lower extremities showed edema of both ankles, feet and legs.

Neurologic examination was rather unsatisfactory. All the deep reflexes were absent. Over the region of the fourth and fifth ribs there was a herpetic eruption.

Laboratory Observations.—Roentgen examination showed old calcareous deposits in the right apex and hilar region. There was evidence of fluid in the left side of the chest. Inoculation of the pleural exudate into a guinea-pig gave negative results. All other laboratory examinations were negative.

Anatomic Diagnosis.—The diagnosis was generalized lymphosarcomatosis, hydrothorax, bilateral hydro-ureter and hydronephrosis.

Autopsy.—Gross Examination: In the region of both parotid glands, firm masses were felt which were continuous with bulgings in the submaxillary, posterior cervical region and supraclavicular nodes, forming a complete collar around the neck. Over the lower lobe of the right lung both pleurae were thickened and separated by an edematous, infiltrating, fibrous tumor which invaded the parenchyma of the lung only at the hilus, surrounding the larger vessels and bronchi and extending several centimeters into the depth of all three lobes. From the region of the hilus the tumor extended from the base of the skull to the coccyx, along the lateral surfaces of the bodies of the vertebrae, and filled the pelvis covering its lateral walls, surrounding in its course the aorta, ureters, nerve fibers, pelvic vessels and organs. In addition, the tumor had extensively infiltrated the omentum, appendix and cecum. The glands in the root of the mesentery and around the celiac axis, axillary and inguinal nodes were also replaced by tumor.

Microscopic Examination: The microscopic structure of the tumor was somewhat similar to that described in case 1. During the removal of the spinal cord,

a continuous sheet of tumor tissue was found along the right lateral surface of the spinal canal adherent to the vertebrae and the dura. The tumor tissue apparently had grown into the canal through the intervertebral foramina.

Sections of the spinal cord of the midthoracic region showed (fig. 2) the tumor mass situated extradurally. The vessels of the cord were slightly thickened and congested. On one side the nerve roots were infiltrated by the tumor cells. In places the dura was replaced by the tumor, which grew in two directions. The spinal cord, with the exception of the roots, did not show any marked signs

Fig. 2.—Midthoracic section of cord showing lymphoid mass situated extradurally. Van Gieson stain; × 30.

of compression. The microscopic appearance of the tumor tissue conformed to the microscopic observations of the tumor found elsewhere in the body.

The symptoms in this case began one and one-half years before admission to the hospital with rapid progression. With the exception of the herpes zoster caused by the invasion of the nerve roots, the neurologic signs were rather scanty in spite of a definite extramedullary

neoplasm. The deep roentgen treatment caused disappearance of the glandular enlargement and gave the patient some relief from his symptoms.

CASE 3.—J. K., a man, aged 32, a salesman, was admitted to the Montefiore Hospital on April 11, 1921. In October, 1920, the patient began to cough and expectorate greenish sputum, which symptoms subsided in January, 1921. Following this he noticed a gradual numbness of the neck, arms, back, chest, abdomen and legs. He had formication limited to the upper extremities, left lumbar region of the abdomen and the feet when in motion. There was a gradual loss of weight and wasting of muscles. During the last month before admission to the hospital he had considerable difficulty in walking, ataxia, constipation and frequency in micturition.

Examination.—The patient was markedly emaciated and pale and had a slight exophthalmos. On percussion, the chest showed dulness of the apex posteriorly and flatness down to the sixth rib. The breath sounds on the right were diminished anteriorly to the third rib and were absent posteriorly. All the other organs were normal.

On neurologic examination, the pupils were found to be dilated and slightly irregular, reacting to all stimuli. There was nystagmus in all directions. There was nutritional atrophy of all the muscles of the body. The upper and lower extremities were markedly ataxic. There were athetoid movements of the fingers. All the deep reflexes, such as the biceps, triceps, knee and ankle reflexes could not be elicited. The lower abdominal reflexes were absent. The cremasteric reflex could not be elicited on the right. The Babinski sign, allied reflexes and ankle clonus were absent. There was loss of position and vibratory sense up to the fourth dorsal segment. There were hypalgesia and hypesthesia from the sixth dorsal vertebra down with vague sensory disturbances above the sixth segment and a suggestion of a belt of hyperalgesia between the fourth and the sixth segments.

Laboratory Observations.—Roentgen examination of the chest showed the lower one third of the right lung completely obscured by a dense homogeneous shadow suggesting a neoplasm. The blood count showed: hemoglobin, 80 per cent; red blood cells, 3,520,000; white blood cells, 12,800. The differential count was normal. All other laboratory data were negative.

Course.—The patient received numerous administrations of deep roentgen therapy. During the early course of the treatments, there was a disappearance of the enlarged glands and some of the symptoms, especially the pain. Later the glands enlarged and failed to respond to treatment, and the patient died on May 28.

Diagnosis.—The diagnosis was: neoplasm of the right lung with secondary deposits in the cord. There was a possibility of subacute combined degeneration. The anatomic diagnosis was: lymphosarcoma of the root of the right lung, bronchopneumonia and empyema.

Autopsy.—Gross Examination: The lower lobe of the right lung, near the hilus, showed a cauliflower-like mass projecting beyond the pleural surface. At the root of the lung there was a hard, white tumor mass roughly 7 cm. in diameter which had eroded and completely obstructed the hyparterial bronchus. The two lower lobes were riddled with cavities varying in size from 0.5 to 2 cm., filled with a foul-smelling, dark yellowish-green, purulent material. The peribronchial lymph glands were soft and enlarged.

The microscopic appearance of the tumor tissue was that of a lymphosarcoma.

Numerous extramedullary lymphoid masses were deposited in the posterior portion at various levels of the spinal cord, chiefly in the upper thoracic region.

Microscopic Observations: Sections of the spinal cord at this level showed a degeneration (fig. 3) of the posterior column and posterior roots. Under the low power lens the process resembled the involvement seen in tabes dorsalis. With special stains and higher magnification the changes of the posterior columns were seen to be the same as those found in compression of the cord. With victoria blue stain, isomorphous gliosis was found instead of condensation of the glial elements as seen in tabes dorsalis.

Microscopic Diagnosis.—The diagnosis was: compression of the cord causing degeneration of the posterior columns.

The duration of illness in this case was nine months, with predominance of the neurologic signs. The absent deep reflexes and the definite signs of the posterior column suggested a diagnosis of tabes dorsalis. The definite sensory level precluded such a diagnosis. The

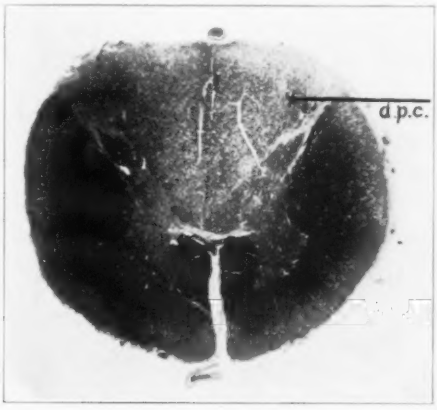

Fig. 3.—Section of thoracic region of cord showing degeneration of the posterior columns (*d.p.c.*). Weil stain; × 30.

gross microscopic picture was that of tabes; examination with higher magnifications showed the condition to be a degeneration due to compression, with the absence of condensation of glial fibers as seen in tabes and multiple sclerosis as shown by Weil and one of us[7] (Davison).

Case 4.—J. H., a man, aged 45, a bookkeeper, was admitted to the Montefiore Hospital on Feb. 11, 1929. In April, 1927, he had noticed an enlargement of the glands of the right groin, which on deep roentgen treatment disappeared within from two to three weeks. In October, 1928, a large gland appeared in the left side of the neck, followed by diplopia, paresis of the left abducens muscle and bilateral optic neuritis. Shortly after a left supranuclear facial and oculomotor

7. Weil, A., and Davison, C.: Changes in the Spinal Cord in Anemia, Arch. Neurol. & Psychiat. **22**:966 (Nov.) 1929.

paresis occurred, which improved ten days following deep radium therapy. The glandular nodules also showed temporary recession. During the course of the roentgen therapy, a crop of subcutaneous nodules appeared; the patient was then admitted to the hospital. Subsequently he developed a weakness of the entire left side of the body and a hypesthesia over the left side of the face and tongue.

Examination.—Physical examination revealed a markedly emaciated man, presenting numerous discrete tumor nodules involving the cranium and the cervical, axillary and inguinal glands. The glands were discrete and freely movable, varying in size from that of a pea to that of a large hazelnut. Those that were primarily intracutaneous were firm in consistency. The heart and lungs were

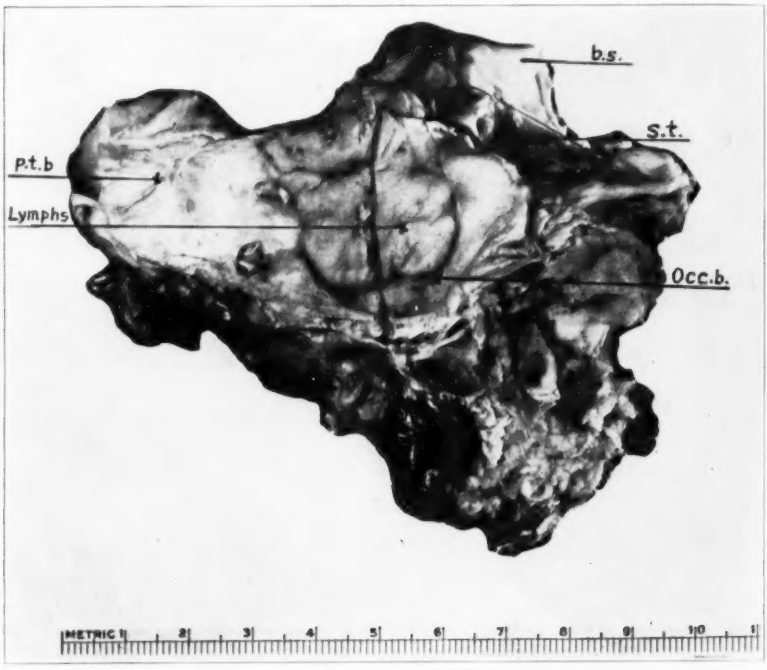

Fig. 4.—Lymph node occupying part of the basilar portion of the occipital bone and the left posterior surface of the petrous portion of the temporal bone. *b.s.* indicates the body of the sphenoid; *s.t.*, the sella turcica; *occ.b.*, the basilar portion of the occipital bone; *p.t.b.*, the posterior surface of the petrous portion of the temporal bone; *lymphs.*, lymphosarcoma.

normal. The liver was enlarged four fingerbreadths below the right costal margin and presented a large, irregular, nodular mass below the free edge. Perianal nodules were present. There was localized tenderness over the upper part of the left femur and over the left scapula posteriorly.

Neurologic examination revealed blurring of the margin of the left disk on the nasal side, weakness of the left external rectus and a suggestion of anisocoria.

There was hypalgesia of the first and second portions of the left fifth nerve without involvement of the motor portion. All the tendon reflexes on the left were definitely diminished. There were no abnormal reflexes. There was generalized muscular wasting with a weakness of the left side of the body, more marked in the upper than in the lower extremities.

Laboratory Observations.—Roentgen examination of the skull disclosed a small area of bone absorption in the parietal region, possibly metastatic. There were pulmonary metastases, and the mediastinal glands were enlarged. A biopsy taken on Feb. 16, 1929, showed the mass to be a lymphosarcoma.

Course.—During the patient's stay in the hospital, he received four deep roentgen treatments, chiefly for the alleviation of the excruciating lumbosacral pain. The only effect was temporary recession of the glandular nodules. Irra-

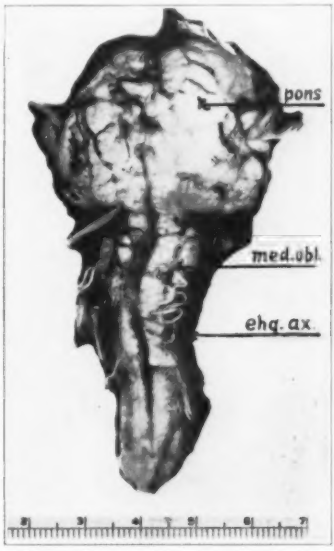

Fig. 5.—Distortion of the pons (*pons*) and medulla oblongata (*med. obl.*) due to compression by the lymph nodes as shown in figure 4. Change in the axis (*chg.ax.*) of the medulla oblongata due to compression.

diation of the cervical and upper dorsal spine had no effect. Typhoid vaccine was also administered without any results. A biopsy taken in February showed the tumor to be a lymphosarcoma. The patient died on March 10.

Diagnosis.—The diagnosis was general lymphosarcomatosis with involvement of the meninges at the base of the skull, extending from the middle fossa downward. The anatomic diagnosis was lymphosarcoma with metastases to all the organs and invasion of the sella turcica.

Autopsy.—Gross Examination: All the lymph nodes were enlarged and readily palpable. Irregular swellings were palpable on the top of the cranium. The paravertebral and prevertebral lymph nodes were everywhere markedly enlarged

and firmly fused with their adjacent glands. In the calvarium several irregular thickenings were fused to the periosteum. In the left wall of the sella turcica a lymph node occupied part of the basilar portion of the occipital bone and the left posterior surface of the petrous portion of the temporal bone (fig. 4). This mass compressed and distorted the pons and medulla oblongata (fig. 5). Another lymph node continuous with the former occupied the portion of the left anterior surface of the petrous portion of the temporal bone and the left sphenoid bone at the clinoid process (fig. 6). When the tumor mass was sawed through, the bony structure was found to be invaded by the lymphosarcoma. Near the foramen magnum there was another small lymphoid mass attached to the dura.

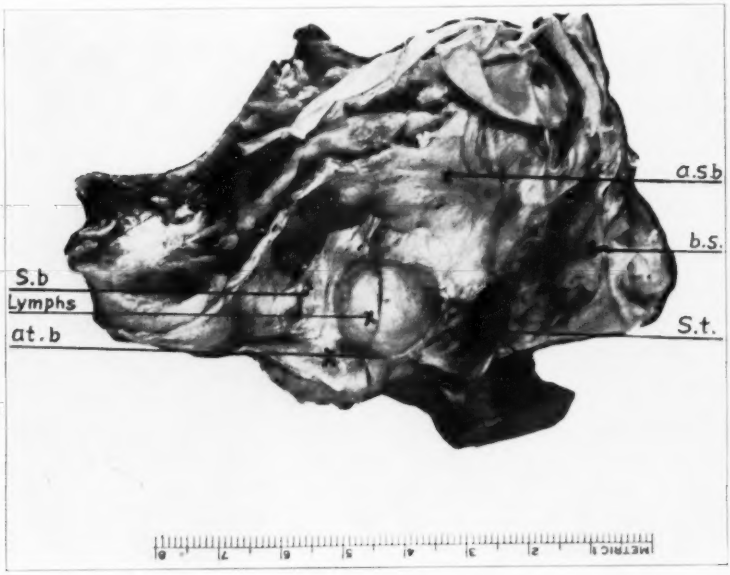

Fig. 6.—Lymph node occupying the left anterior surface of the petrous portion of the temporal bone and left sphenoid bone. *a.s.b.* indicates the alae of the sphenoid bone; *b.s.*, the body of the sphenoid; *s.t.*, the sella turcica; *s.b.*, the sphenoid bone; *a.t.b.*, the anterior surface of the petrous portion of the temporal bone; *lymphs.*, the lymphosarcomatous nodule.

The brain, with the exception of a depression of the left side of the temporal lobe caused by the tumor mass, appeared to be normal on the surface. When the brain and the spinal cord were sectioned, no abnormalities were observed.

Microscopic Examination: Examination of the tumor mass of the skull showed it to be a lymphosarcoma. Sections of various regions of the brain stained by special preparations revealed no abnormalities.

The left side of the pons showed a marked flattening, especially at the exit of the trigeminal nerve (fig. 7). With the Weil method, no areas of demyelination were observed, with the exception of part of the fibers of the fifth nerve

on the left side. With the hematoxylin and eosin and cresyl violet methods, the nerve cells of the nuclei of the fifth nerve showed a slight amount of pigment atrophy. The nerve cells of the sensory portion of the left fifth nucleus were somewhat atrophic and shrunken, and the Nissl substance stained poorly with the selected stains (figs. 8 and 9). A few nerve cells of the nucleus of the left sixth nerve showed similar changes.

Sections from the cervical region of the cord showed some of the cells of the anterior horns, especially the dorsolateral group, to be slightly swollen, with a disappearance of the Nissl substance.

Microscopic Diagnosis.—The diagnosis was lymphosarcomatous invasion into the skull causing compression of the pons and medulla oblongata.

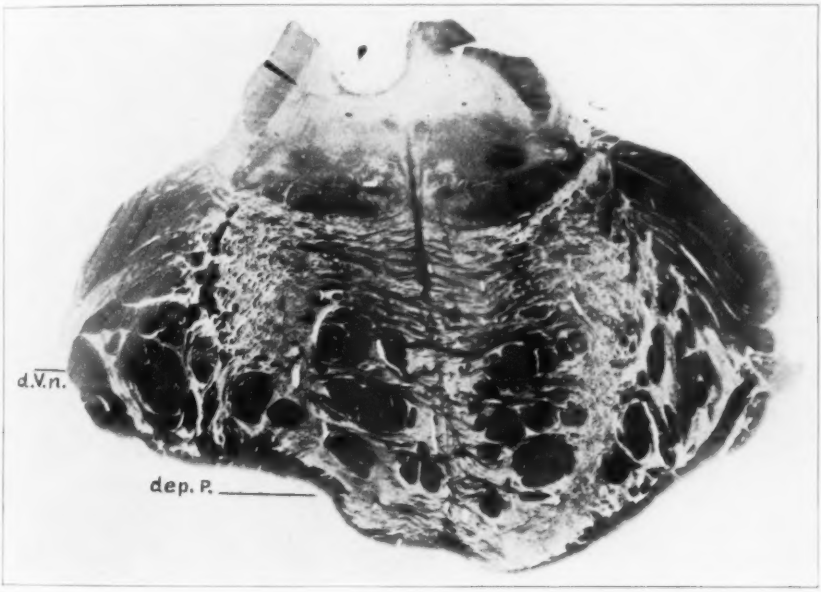

Fig. 7.—Flattening of the left side of the pons. Demyelination of the fifth nerve (*d.V.n.*); depression of the pons (*dep.p.*) from the compression of the lymphosarcomatous nodule.

The tumor masses found in the other organs revealed the same microscopic characteristics as the metastasis to the skull.

The important features of this case were: the recession of some of the lymph glands without deep roentgen treatments and the involvement of the skull, especially of the middle and posterior fossa. The anisocoria was probably due to the compression of the left cervical sympathetic by the tumor. The sensory changes of the left fifth and the left external rectus palsy were due to secondary changes in the nuclei of those nerves due to compressions, as illustrated in figures 7, 8 and 9. The duration of the disease in this case was about two years.

Group 2: Cases of Lymphosarcoma Presenting Neurologic Signs Which Did Not Come to Autopsy.—Case 5.—E. L., a man, aged 64, was admitted to the Montefiore Hospital on April 18, 1922. Following a toothache in September, 1921, a large swelling occurred on the opposite side of the face and neck. A biopsy from this swelling was diagnosed as tuberculosis. In January, 1922, a piece of tissue from the same area was diagnosed as lymphosarcoma. Since then the patient had difficulty in breathing and choking sensations. He received several treatments with radium followed by diminution in the size of the tumor

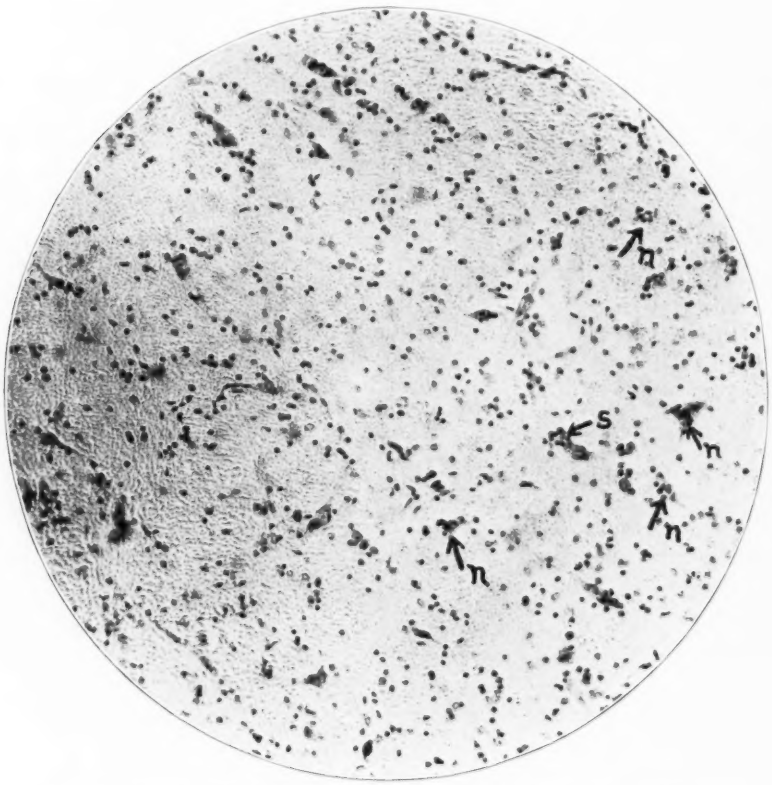

Fig. 8.—Section from the sensory portion of the nucleus of the fifth nerve showing degeneration of nerve cells. *n* indicates neuronophagia; *s*, satellitosis. Cresyl violet stain; × 300.

and disappearance of the difficulty in swallowing. In June, he had diplopia and disturbance in vision of the right eye, followed by insomnia and generalized weakness.

Examination.—Physical examination revealed an emaciated, anemic looking man. A large, hard mass bulged from the right side of the pharynx into the right pharyngeal cavity. The uvula was displaced to the left, its upper pole

reaching the level of the palate. The movements of the neck were limited and painful. There was a large swelling on the right side of the neck. Both supraclavicular fossae showed enlarged glands, firm in consistency. The movements of the right side of the chest were limited with an area of dulness in the left axillary region below the sixth rib. The breath sounds were normal. The liver was enlarged.

Neurologic examination showed a slight tic of both eyelids, more marked on the right. The pupils were irregular and reacted somewhat sluggishly to light,

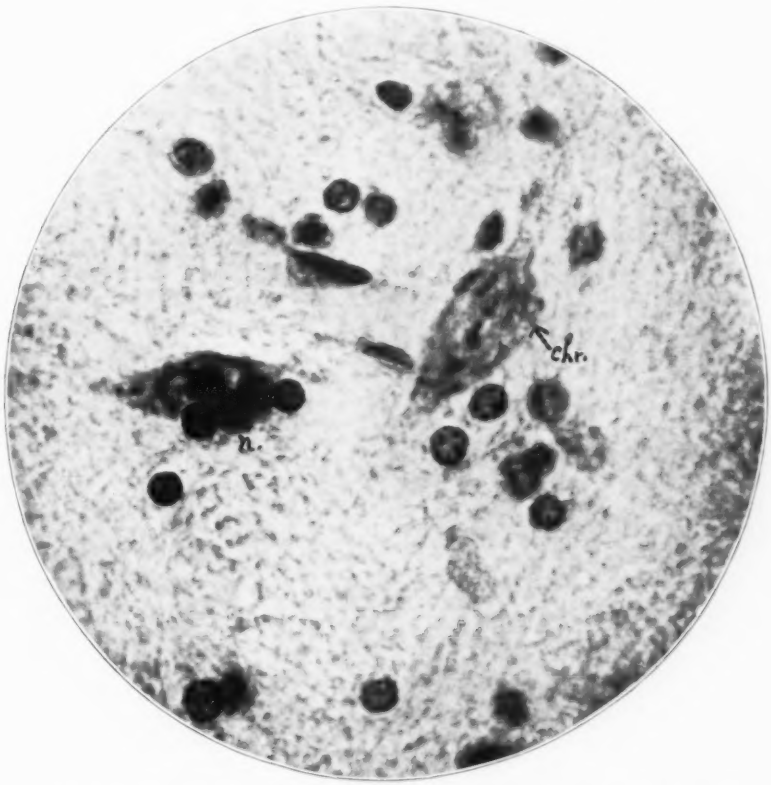

Fig. 9.— Same as figure 8 under higher magnification, × 800, showing degeneration of the nerve cells and disappearance of the Nissl substance. *chr.* indicates chromatolysis; *n.*, beginning neuronophagia.

but well in accommodation. There was paralysis of the right external rectus. There was corneal hypesthesia on the right side. The tongue deviated to the right. The left margin of the tongue was definitely thinner than the right, with fine fibrillary twitchings. There was apparently no paralysis of the palate or uvula. Hearing on the right side was diminished, bone conduction being better

in the right ear. The entire musculature of the body showed general wasting and poor tonus. All the deep reflexes were present and equal on the two sides.

Laboratory Observations.—The blood count showed: red blood cells, 3,300,000; white blood cells, 6,000; hemoglobin, 80 per cent; the differential count was: polymorphonuclear leukocytes, 70 per cent; small lymphocytes, 2 per cent; large lymphocytes, 22 per cent; eosinophils, 6 per cent.

The roentgenogram showed small areas of infiltration in both apexes and an old thickened pleura in the left base.

Course.—The patient was in the hospital at various intervals, where he received twenty-nine applications of radium. The general condition of the patient was improved, and the tumor decreased in size, enabling him to eat and to return to his work. The enlargement recurred at times. He has not been heard from since November 27.

Diagnosis.—The diagnosis was lymphosarcoma with invasion of the dura in the posterior fossa causing compression of the cranial nerves.

This case presented early involvement of the cervical lymph nodes, with definite involvement of the nervous structures in the posterior fossa. The general physical signs as well as the neurologic symptoms disappeared following intensive radium therapy. The patient has not been heard from since 1922. This case falls in the same group as case 4, group 1.

CASE 6.—L. C. R., a man, aged 37, a contractor, was admitted to the Montefiore Hospital on July 11, 1922. In April, 1922, the patient had experienced a dull, dragging sensation in the left side of the abdomen radiating to the back and the left hypogastric region. The abdominal pains became worse, and in May an exploratory laparotomy was performed at which time a retrocecal, kinked appendix was removed without relieving the patient from his symptoms.

In April, 1921, he had dysentery, with a temperature of 102 F.

Examination.—Physical examination showed a chronically ill patient in great pain, with an enlargement of the cervical and submaxillary glands. The heart, lungs and all other organs were normal.

Neurologic examination showed an area of hyperalgesia between the ninth and tenth dorsal segments on the left side, confined to the anterior divisions of the posterior roots, i. e., beginning anteriorly about the midline and terminating at the postaxillary line. There was tenderness over the eighth, ninth and tenth dorsal vertebrae. With the exception of lively achilles' reflexes and a suggestive ankle clonus on the left, all the other observations were negative.

Laboratory Observations.—Roentgen examination of the chest showed a dense uniform shadow over the entire left side. The structure of the lung in back of this shadow could not be distinctly seen, but there was apparently some infiltration in the region of the lower lobe.

On July 20, 45 cc. of clear spinal fluid was removed under increased pressure. There were 30 cells, mostly lymphocytes. The fluid showed a slightly positive globulin reaction and a faint reduction with Fehling's solution. A microscopic examination of pleural exudate revealed tumor cells.

Course.—Following a diagnosis of an extramedullary tumor of the spinal cord, the patient was sent to the Neurological Institute, where a laminectomy was performed by removal of the eighth, ninth and tenth dorsal vertebrae, without finding any pathologic process at this level. The ninth, tenth and eleventh left

posterior roots were divided for relief from pain. Three weeks later, he developed pleurisy on the left side of the chest with painful respiration and elevation of temperature. The observation on the chest showed a pleural effusion, but on aspiration fluid was not obtained. The patient was readmitted to the Montefiore Hospital in October, at which time he received applications of deep roentgen and radium therapy without any benefit. He died on October 24.

Diagnosis.—The diagnosis was lymphosarcoma with metastases to various organs and the vertebral column.

In this case the mass was chiefly confined to the chest, with later involvement of the cervical lymph nodes. The diagnosis of lymphosarcoma was arrived at clinically. Autopsy was not done. The neurologic signs, especially the excruciating pains, were due to metastasis to the vertebrae which caused pressure on the roots. The administration of deep roentgen or radium therapy failed to alleviate the symptoms.

Case 7.—L. S., a woman, aged 38, was admitted to the Montefiore Hospital on Nov. 14, 1922. In March, 1922, she had noticed a painless but annoying swelling of the left tonsil. Tonsillectomy was done in April, followed a week later by a swollen gland in the left submaxillary region. In August, a tumor, the size of a hen's egg, was removed below the left ear. A month later, the swelling became markedly enlarged causing dysphagia. Following the administration of radium combined with deep roentgen therapy, a slight improvement was noticed. In November, there was a recurrence of the swelling and of the symptoms with severe pains radiating from the left side of the neck down to the arm. In the interim, she lost 25 pounds (11.3 Kg.).

The past history was unimportant.

Examination.—Physical examination showed the patient to be fairly well nourished with a tremendous swelling of the left side of the face, extending posteriorly below the concha and occiput into the spines of the cervical vertebrae, with a subjective sensation of choking, inspiratory stridor and nasal speech. The left eye could not be closed completely; the mouth could not be opened for a distance greater than 1 cm., and the tongue could not be protruded. The heart, lungs and abdomen were normal. Two small draining sinuses were present. The left clavicle could not be palpated.

Neurologic examination revealed a left peripheral facial paresis with a questionable paresis of the left fifth motor nerve. There were apparently no sensory disturbances. The left upper extremity was extremely tender and could not be moved. The left biceps and triceps reflexes were absent. All other reflexes were normal.

Laboratory Observations.—The urine was positive for albumin, with many red and white blood cells. A biopsy at the Memorial Hospital showed the mass to be a lymphosarcoma. The roentgenogram showed evidences of metastases in the lower dorsal spine. All other laboratory data were negative.

Course.—The patient was in the hospital for only four days, during which time she received one treatment with radium without any benefit. She developed dyspnea and cyanosis and died on November 19.

Diagnosis.—The diagnosis was lymphosarcoma of the neck.

The only neurologic sign presented in this case was a peripheral involvement of the left facial nerve with a questionable involvement of

the left brachial plexus. The roentgenogram showed evidences of metastases to the lower dorsal spine.

COMMENT

An analysis of twenty-six cases of lymphosarcoma from the Montefiore Hospital since 1922 showed seven cases with involvement of the central nervous system. Of nine cases that came to autopsy, four showed lesions of the central nervous system. Fifteen of the twenty-six patients were males and eleven females. Their ages ranged from 36 to 60, the average being 45 years. The oldest patient was 74, the youngest 11 years. The average life from the onset of the disease in the cases presented was one year and ten months. The longest duration of the disease in one case was seven years, and the shortest five months. Twenty-three of the patients died, two are still living and one could not be followed up. Desjardins and Ford,[8] in an analysis of fifty-five patients with lymphosarcomas who died, found the average duration of the disease from the onset of symptoms to be two years and five and one-half months.

Two of the seven cases showing neurologic signs showed invasion (cases 4 and 5) of the cranial cavity localized chiefly in the middle and posterior fossae; four showed involvement of the vertebral column or the spinal meninges which caused compression of the spinal cord or the posterior roots, resulting in herpes zoster (as in case 2), and one case showed involvement of the facial nerve peripherally (case 7). Woltman,[9] in a series of tumors of the nasopharynx, reported six cases of lymphosarcoma with involvement of the cranial nerves, but none of these cases came to autopsy. Our series of cases showing secondary compression of the spinal cord or the posterior roots is the largest, the only other case reported being that of Guillain.[5]

Cases 4, 5 and 7 showed early involvement of the cervical lymph nodes, in two (cases 4 and 5) of which the cranial cavity was invaded. In the other cases, the invasion of the glands of the neck did not occur until late in the disease.

In case 4, in which the cranial cavity was invaded, the brain tissue itself did not show any evidences of invasion by the lymphosarcoma, as is usually seen in metastasis from other tumors, especially metastatic carcinomas. The invasion in this case took place by way of the lymphatics. As the brain proper is not supplied by lymphatics, this readily explains the absence of invasion of the brain tissue by lymphosarcomas or Hodgkin's disease. The cases showing involvement of the spinal

8. Desjardins, A. U., and Ford, F. A.: Hodgkin's Disease and Lymphosarcoma, J. A. M. A. **81**:925 (Sept. 15) 1923.

9. Woltman, H. W.: Malignant Tumors of the Nasopharynx with Involvement of the Nervous System, Arch. Neurol. & Psychiat. **8**:412 (Oct.) 1922.

cord in the form of compression did not show enlarged cervical lymph glands until late in the disease. In none of these cases was the spinal cord directly involved.

All of the seven patients treated by deep roentgen and radium therapy, with the exception of the patient in case 7, showed a recession of the lymphosarcomatous masses with improvement in the symptoms only early in the treatment. After a few treatments, the enlargements and symptoms recurred and finally failed to respond. This is characteristic of all lymphosarcomas.

CONCLUSION

Twenty-six patients with lymphosarcoma admitted to this institution since 1922 were investigated, seven of whom presented neurologic signs and symptoms. Four of these patients showed signs of compression of the spinal cord. The literature on this subject reports only one case.

In none of the cases was there a direct invasion of the brain or the spinal cord. The symptoms were due chiefly to compression from invasion of the skull, vertebrae or meninges.

Invasion of the cranial cavity took place only when the cervical lymph nodes were involved, and, as observed in our series, involved early.

Deep roentgen and radium therapy, while not a cure for the disease, causes some relief from the symptoms during the first few applications. The relief is due chiefly to the recession of the tumor, which causes compression on the respective organs. When these enlargements fail to respond to treatment, improvement in the symptoms may not be expected. For a time, however, these patients benefit a great deal by deep roentgen or radium therapy, and at present these are the best forms of palliative treatment.

SPONTANEOUS RECOVERY FROM PERFORATION OF PEPTIC ULCER INTO THE FREE ABDOMINAL CAVITY *

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Spontaneous recovery following perforation of a peptic ulcer into the free abdominal cavity is and has been generally considered of rare occurrence. Older writers attempted to account for the occasional recovery without operation by the absence of food in the stomach at the time rupture occurred. Thus, Hall,[1] who reported one and collected six additional cases of spontaneous recovery, ascribed the outcome to the empty state of the stomach when the perforation took place. He concluded, "When perforation of a presumably full stomach has occurred laparotomy affords probably the only chance." Pariser [2] was also greatly impressed by the importance of the presence or absence of food in the stomach in determining the fate of a perforated ulcer. In fact, he recommended considering as the time of onset in the case of a fasting stomach not the moment of actual perforation but the time food or liquid was ingested subsequent to rupture. The clinical investigation of Brunner [3] cast doubt on the belief that death was imminent unless the stomach was empty at the time of perforation. Brunner was able to collect several cases in which recovery supervened, although the stomach was not entirely devoid of food when perforation occurred. He agreed, however, that spontaneous recovery after perforation into the free abdominal cavity was quite exceptional, stating that it occurred at the most in 5, and in all likelihood, a much smaller percentage of cases in which operation was not performed. Speck,[4] in a more recent comprehensive review of the subject of perforation of peptic ulcer into the free abdominal cavity, stated that according to the new statistics only one or two of every hundred patients recover spon-

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1. Hall, W. W.: A Case of Perforating Gastric Ulcer: Peritonitis: Recovery, Brit. M. J. **1**:64, 1892.

2. Pariser, C.: Zur Behandlung des frei in die Bauchhöhle perforierten Duodenalgeschwür, Deutsche med. Wchnschr. **21**:450 and 466, 1895.

3. Brunner, F.: Das acut in die freie Bauchhöhle perforierende Magen- und Duodenalgeschwür, Deutsche Ztschr. f. Chir. **69**:101, 1903.

4. Speck, W.: Zur Klinik und Pathologie der in die freie Bauchhöhle perforierten Magen- und Duodenalgeschwüre, Beitr. z. klin. Chir. **129**:537, 1923.

taneously. Practically all modern textbooks and systems, not only of surgery but also of medicine, voice essentially the opinion expressed by Speck.

A few years ago, following routine study of a series of patients with acute abdominal pain, I arrived at the conclusion that death from ulcer was by no means the invariable outcome when operation was not performed. As my experience increased, I became more and more impressed by the belief that recovery without operation following perforated peptic ulcer was not of infrequent occurrence. At first with timidity, but later with assurance, I made the clinical diagnosis of perforated ulcer with spontaneous recuperation in cases in the wards. Since my associates repeatedly questioned the correctness of this diagnosis, I decided to record and collect the records of the cases which I considered instances of spontaneous recovery following perforation into the general abdominal cavity. Through the courtesy of my colleagues on the staff at the Cook County Hospital, I was privileged to use the material in the several medical and surgical wards. Within a period of approximately eighteen months, beginning with the spring of 1928, I observed forty cases in which the diagnosis of spontaneous recovery seemed warranted. In all probability, there were treated in the hospital during the same period other patients with more or less identical cases, who, however, did not come under my observation.

The cases gathered in the course of this study can be conveniently arranged in four groups. The first group includes those cases of ruptured ulcers in which the presence of a perforation recently obturated, sealed or covered, was demonstrated at operation undertaken within a short time after the accident occurred. The second group comprises cases of chronic ulcer in which an antecedent history of acute perforative peritonitis was obtained, and in which at operation, performed after a lapse of time, old adhesions, presumably due to a previously perforated ulcer, were found. In the third group are cases with the history of a chronic ulcer, signs and symptoms of perforation and the presence of free intraperitoneal air demonstrated by means of roentgenograms shortly after the onset of acute symptoms. In the fourth group, both operative and roentgen evidence of a ruptured viscus is lacking, the diagnosis being based on the history of a chronic ulcer, the clinical symptoms and signs of a perforative peritonitis and the roentgenologic demonstration after subsidence of the acute symptoms of a gastric or duodenal lesion. The evidence for considering the cases in all four groups as instances of free perforation with spontaneous healing is submitted here together with case reports. To avoid unnecessary repetition, since some of the cases are practically identical, not all of the forty cases are described. Twenty cases, five from each group, selected to represent the most diversified in the series, seem sufficient for illustrative purposes.

Only the data that deal directly with the phase of ulcer under consideration are included in the following case reports. It should be constantly borne in mind that the history as subsequently recorded represents in many instances the wheat sifted from a great deal of chaff. In a considerable proportion of the cases, the information volunteered by the patient and the history as written by the intern bore little resemblance to the anamnesis. Direct questioning, after the physical observations led to the suspicion of a perforated ulcer, in not a few cases was the means of obtaining the characteristic history presented to the reader.

GROUP 1: EARLY OPERATIVE EVIDENCE OF PERFORATION

Recoveries from perforated ulcer without operation are not rare in the surgical literature. These spontaneous recuperations, it is generally believed, are conditioned by the presence of a preformed sac of adhesions. It is assumed that the adhesions develop just prior to perforation as they do in appendicitis. Since it requires a certain amount of time for the production of delimiting membranes, perforations in which walling-off occurs are usually designated as subacute to distinguish them from the free perforations which are generally considered to be acute. The clinical history of prodromes (inaugural symptoms of Moynihan [5]), which frequently usher in the manifestations of actual rupture in cases of spontaneous recovery, is generally assumed to correspond to a preperforative stage, during which time the adhesions form.

The conception of subacute perforation as previously described is, however, not supported by an unprejudiced analysis of the facts. In the first place, pathologico-anatomic evidence to support the idea of a true subacute perforation is lacking. Recent, delimiting adhesions which are older than the perforation have been neither demonstrated to me by my surgical colleagues nor described in reports in the literature so far as I can ascertain. If they occur, they do so exceptionally. The exudate and its products in all the cases I have had the opportunity to observe, unless due to a previous rupture, are more recent than the perforation. What determines the limitation of degree and extent of the peritoneal soiling is not the presence of a preformed sac but the early spontaneous closure of the perforation. A frequent phenomenon which restricts the escape of gastroduodenal content into the free abdominal cavity is, as pointed out by Schnitzler,[6] the covering of the hole by an adjacent

5. Moynihan, B. G. A.: Duodenal Ulcer, ed. 2, Philadelphia, W. B. Saunders Company, 1912.

6. Schnitzler, J.: Ueber gedeckte Magenperforationen und über die Entstehung der penetrierenden Magengeschwüre, Med. Klin. **1**:938, 1912.

structure, particularly the liver. Sealing the leak by plastic exudate, plugging the hole by omentum (Moynihan[8]) and obturation by food particles are other methods which nature employs singly or in combination to effect a spontaneous cure. From the clinical standpoint, the foundation for the present notion of subacute perforation is likewise weak. Premonitory symptoms, which are said to be characteristic of a slow type of perforation, are not infrequently absent in cases in which recovery occurs spontaneously. Further, if careful inquiry is made, one is able to elicit prodromal symptoms quite frequently in the so-called acute perforations. As a matter of fact, the mode of onset in the two types of perforation is practically indistinguishable, and it is only the mild course which follows rupture in the "subacute" group which permits differentiation.

If one accepts the view that the cases formerly classified as subacute are actually acute perforations in which the hole in the stomach or duodenum becomes spontaneously sealed, then the number of cases of rupture into the free abdominal cavity, as corroborated by operation, in which spontaneous cure occurs can no longer be considered small. Lund,[7] in 1905, reported three cases of spontaneous closure of perforations which he encountered within less than one year. At the time of operation, undertaken a few days after rupture, the perforation in each case was no longer patent. In 1907, Moynihan[8] reported five cases in which he observed spontaneous closure at laparotomy performed at an early stage following rupture. Schnitzler[9] reported the cases of four patients operated on by him within a period of two years, the perforation in each case being covered by an adjacent viscus. Two cases were observed by Finsterer[9] and several were seen by Aigrot.[10] Case reports in the literature intended for other purposes furnish further examples of spontaneous closure of perforated ulcer demonstrated at the operating table. For example, Kellogg,[11] in reporting a case of spontaneous pneumoperitoneum due to a perforated peptic ulcer, mentioned the circumstance that at the time of operation the hole

7. Lund, F. B.: Subacute Perforation of the Stomach: Report of Three Cases, Boston M. & S. J. **152**:516, 1905.

8. Moynihan, B. G. A.: Subacute Perforation of the Stomach and Duodenum, Am. Surg. **45**:223, 1907.

9. Finsterer, H.: Geheilter Fall von Ulcus duodeni Perforation, Wien. klin. Wchnschr. **28**:1240, 1915; Gedeckte Duodenalperforation, Zentralbl. f. Chir. **49**: 1013, 1920.

10. Aigrot, G.: De l'obturation spontanée de certaines perforations d'estomac en peritoine libre, Presse méd. **35**:35, 1927.

11. Kellogg, W. A.: Spontaneous Pneumoperitoneum Demonstrated by the X-Ray in Acute Gastro-Intestinal Perforations, New York State J. Med. **114**: 294, 1921.

was plugged by a piece of omental fat preventing the further escape of gastric content. Another case of pneumoperitoneum is reported by du Pasquier [12] in which it was recorded in the operative report that the leak in the duodenum had been checked by fibrin and omentum.

Surgical demonstration of spontaneous recovery following free perforation is not limited to the cases in which the plugged or sealed hole is directly observed, but includes also a number of ruptured ulcers in which the surgeon fails to bring the site of perforation into view. Two such groups of cases can be mentioned, the one in which the stomach and the duodenum are explored and the rupture not discovered, and the other in which the upper abdominal organs are not visualized during the course of the laparotomy. In both groups, the presence in the peritoneal cavity of a nonodorous, thin fluid resembling gastric or duodenal contents practically establishes the diagnosis of a perforated ulcer. It is not surprising that a surgeon occasionally fails to disclose a perforation, even though the incision for the exposure of the stomach and duodenum is a suitable one. At the time operation is performed, the hole is not infrequently covered, sealed or plugged, and it is necessary to reopen the hole in order to locate it. The first case of ruptured ulcer I saw in a woman was one in which there was a large quantity of characteristic fluid free in the peritoneal cavity, and yet the surgeon, even after careful exploration of the stomach and duodenum, was unable to find the site of perforation. The drain which was inserted was virtually useless, since practically nothing escaped. The unexpected recovery was astonishingly smooth. Another example of failure to isolate the perforation is summarized in case 4. These and similar cases can reasonably be considered instances of spontaneous recuperation, since operation under these circumstances frequently does nothing but add insult to injury. The drain placed in the region of the stomach accomplishes practically nothing, since the peritonitis is already diffuse and the exudate tends to gravitate to the dependent portions of the abdominal cavity.

The cases of spontaneous recovery from perforated ulcer in which the stomach and duodenum are not exposed at operation are, as a rule, those in which a mistaken clinical and pathologic diagnosis, usually of appendicitis, is made. The fluid erroneously considered appendical exudate is removed, the appendix is amputated and the upper part of the abdomen is not even explored by the unsuspecting surgeon. An instance of this not uncommon mistake is recorded in case 5, and one is related by Wickbom.[13] These errors are rarely reported; neverthe-

12. Du Pasquier, G.: Sur un signe radiologique des perforations d'ulcerés gastriques ou duodénaux, Rev. méd. de la Suisse Rom. **48**:785, 1928.

13. Wickbom, H.: Ist ein sofortiger operativer Eingriff bei perforiertem Magengeschwür stets Notwendig? Acta chir. Scandinav. **64**:43, 1928.

less, but few hospitals of any size lack at least several examples in their history files. Perforations in which closure is difficult but in which tamponading is employed, as recommended by Hoffman,[14] cannot be included as instances of spontaneous recovery from rupture attested to by early operation, but indicate the ability of the adjacent structures to seal a leak in the upper part of the gastro-intestinal tract.

Case 1.—G. J., a colored man, aged 49, admitted to the hospital on Aug. 20, 1928, complained of periodic distress of an ulcerous type of one year's duration. Roentgen examination on the morning of August 30, entailed considerable manipulation of the stomach in an attempt to overcome a pyloric obstruction. That evening, intolerable epigastric pain developed shortly after which vomiting and hiccup occurred. The right upper abdominal quadrant was rigid and tender. Morphine afforded relief. Slight fever and a leukocytosis of 16,000 developed the next day, followed by rapid subsidence of symptoms and signs. Operation performed on September 15 disclosed a perforation of the pylorus securely covered over by the gallbladder, which formed the floor of the ulcer. The texture of the adhesions corresponded to the age of the acute pain experienced sixteen days prior. The perforation was sutured and cholecystectomy and gastro-enterostomy performed. The patient recovered.

Case 2.—F. G., a white man, aged 47, was admitted to the hospital on Oct. 13, 1928, with a typical picture of a perforation which occurred sixteen hours previous to entrance. Laparotomy revealed free air and a moderate amount of thin fluid. The pyloric region was densely indurated and covered by thick fibrinous exudate. The site of perforation was not found. Gastro-enterostomy was performed, and a single drain inserted. There was practically no drainage from the wound. Complete recovery followed.

Case 3.—J. N., a white man, aged 49, was admitted to the hospital on Dec. 26, 1928, with the clinical picture of a perforated ulcer. During the week prior to the development of the acute symptoms, there was an aggravation of the previous, mild symptoms of ulcer. Laparotomy performed about twenty-four hours after onset showed duodenal contents in the abdominal cavity and the liver, gallbladder and omentum bound to the duodenum by fibrinous adhesions to form one large mass. Sudden collapse of the patient led to a hasty closure without an attempt to isolate and suture the opening. After a stormy convalescence, the patient recovered completely.

Case 4.—J. D., a white man, aged 30, entered the hospital on Jan. 13, 1929, thirty-six hours after he was seized by severe epigastric pain. There was only slight rigidity and moderate tenderness over the right side of the abdomen. Perforated ulcer was not diagnosed. At operation, performed on January 18, a week after onset, the pyloric portion of stomach was found attached to the abdominal wall by organizing adhesions which were readily torn. Separation exposed a defect of the gastric wall about which was an area of induration. The perforation was closed and gastro-enterostomy performed. The patient recovered.

Case 5.—H. S., a colored man, aged 40, was admitted to the hospital on March 22, 1929, four hours after the onset of a most agonizing epigastric pain. The

14. Hoffman, A.: Zur Behandlung des perforierten Duodenalgeschwurs, Zentralbl. f. Chir. **38**:1625, 1911.

history, symptoms and signs were typical of perforated peptic ulcer. Through an upper abdominal incision, the stomach and duodenum were explored but no perforation found. There was a moderate amount of free fluid. The appendix was thought to be phlegmonous, and it was therefore amputated. A stab wound was made over McBurney's point, and a drain was inserted. The fluid obtained at the operation had the characteristics of escaped gastric contents (particles of food). The appendix microscopically showed the inflammation to be limited to the serosa. Slow but progressive improvement followed until intercurrent erysipelas resulted in death. Autopsy was not permitted.

GROUP 2: LATE OPERATIVE EVIDENCE OF PERFORATION

The second group of cases includes those in which old adhesions are observed at operation performed some time after an assumed perforation occurred. In some instances, the adhesions are strictly localized about an indurated area in the stomach or duodenum, and the association between the ulcer and healed perigastritis is clear. In other cases, the adhesions are found in remote portions of the abdomen, and in these the relationship between the perforation and the adventitious bands is somewhat conjectural.

With regard to local adhesions, it is often stated that a perigastritis generally results from penetration of infectious material through the intact base of an ulcer. Although this mode of origin of peritoneal adhesions about the base of an ulcer is possible, it is from the practical standpoint quite exceptional. Schnitzler [6] has adduced sufficient operative evidence to establish the contention that perigastric or periduodenal adhesions in general do not precede but rather follow the escape of contents through an actual perforation. If one is willing to accept the claim that a noteworthy degree of fibrous perigastritis or periduodenitis complicating a peptic ulcer indicates a previous perforation, then the number of spontaneous recoveries from perforation, demonstrated by operation performed after a lapse of time, cannot be considered small. For instance, Moynihan,[5] in 1907, reported eight cases of marked local fibrous peritonitis observed at operation at a considerable interval after symptoms of perforation occurred. In three of these cases, an hourglass deformity was found in two, evidences of pyloric obstruction. Wickbom [13] observed five cases of acute perforation in which the upper abdominal operation was postponed. At laparotomy, performed within a few weeks, there were extensive adhesions in the region of the suspected perforation in each instance.

In the case of the more remote adhesions, the basis for assuming a perforated ulcer as the cause is the history of a chronic ulcer with supervening symptoms of acute perforation and the absence of any other causal factor. At times, the adhesions are so located (i. e. between liver and diaphragm) as to lead to no ill effects. At other times, the localization is such as to cause obstruction, as in case 10 of this series.

The origin of abdominal bands or disseminated adhesions is frequently unexplained until a careful history yields evidence of a previous ulcer which has probably long since perforated and sealed spontaneously. One of the most instructive cases of this type was seen at autopsy at the Cook County Hospital, in 1928, by Dr. H. G. Wells, who found in a patient with ascites which was clinically attributed to atrophic cirrhosis, fibrous adhesions, the result of a previous perforated ulcer compressing the portal vein.

Fig. 1 (case 8).—A constant, rigid deformity of the prepyloric area due to adhesions following perforation with spontaneous healing.

CASE 6.—L. S., a white man, aged 21, with an antecedent history of ulcer of fifteen months' duration, was operated on, Dec. 15, 1928. In addition to a duodenal lesion, fibrous adhesions throughout the abdomen, most numerous about the duodenum, were found. A previous perforation was suspected, and the patient interrogated accordingly. It was then learned that on May 6, while on a streetcar, he was seized with an intolerable pain which practically annihilated him and caused him to fall from his seat. He was rushed home in a taxicab. Two hypodermic injections were required before the pain moderated. After the second day, the severe pain subsided. After nine days of confinement, the patient resumed his activities. The details of the acute attack were characteristic of a perforated ulcer.

Case 7.—J. D., a white man, aged 51, was admitted to the hospital on Feb. 8, 1929. His ailment was diagnosed as carcinoma of the stomach because of his marked loss of weight, absence of free acidity (with one Ewald meal only) and a rigid prepyloric deformity (fig. 1). A benign calloused ulcer of the pars media covered by dense omental adhesions was revealed at operation and also extensive adhesions between the stomach and liver. It was learned that the patient had been in the hospital previously. Reference to his old record indicated that he had entered on Sept. 22, 1928, five days after the onset of terrific pain which persisted until shortly before admission. Roentgen examination undertaken a few days later demonstrated a penetrating ulcer with a spastic incisura. Close questioning

Fig. 2 (case 8).—A semilateral view taken almost five months before figure 1 and twelve days after the onset of severe abdominal pain. The arrows point to an area of radiolucence due to intraperitoneal air located between the right dome of the diaphragm and the upper surface of the liver.

yielded a clinical history typical of perforated ulcer. On reexamination of the old films, air could be discerned beneath the dome of the right side of the diaphragm (fig. 2), strong light being required to render the radiolucence apparent. The presence of a perforation indicated by the pneumoperitoneum had been overlooked during the first admission.

Case 8.—W. B., a white man, aged 66, entered the hospital on May 16, 1929, with the symptoms, signs and roentgen indications of a duodenal ulcer and a subacute obstruction of the small intestine. An inquiry into the past history with particular reference to attacks of unusually violent pain elicited the information

that on Aug. 6, 1928, following a meal of steak and onions, the patient suffered excruciating pain, which appeared abruptly and almost annihilated him. A hypodermic injection was followed by a diminution in the intensity of the pain. After twelve hours it was no longer severe, and after twenty-four hours the pain had subsided. The patient responded to medical treatment for ulcer and entered the hospital on account of the supervention of symptoms of subacute intestinal obstruction. The patient died rather unexpectedly while under observation. Autopsy revealed an indurated duodenal ulcer attached to which was the liver and omentum. There were a number of adventitious fibrous bands, one of which had produced strangulation of a loop of ileum. No other cause for the healed peritonitis than the assumed ulcer perforation was discovered.

Case 9.—J. L., a white man, aged 42, was admitted to the hospital on June 13, 1929, following a brisk gastro-intestinal hemorrhage. Operation on June 20 disclosed an intimate adherence of the duodenum to the gallbladder together with numerous adhesions about the pyloric portion of the stomach. After separation was accomplished, the wall of the gallbladder was found to form the base of a calloused duodenal ulcer. An antecedent perforation, closed by apposition of the gallbladder, was presumed, and the patient questioned later with this in mind. He related that in 1922, for a few days prior to Christmas he suffered from symptoms of ulcer of an aggravated character. On December 26, while driving a wagon, he was seized with excruciating knifelike pains located in the upper part of the abdomen and passing to the back. He managed to reach home with extreme difficulty half an hour later, but he was so prostrate that it was necessary to carry him into the house. One hypodermic injection administered by a physician had little effect. A gradual abatement of pain occurred during the course of the next eight days, although excruciating pain appeared with change of position during this time.

Case 10.—J. B., a well preserved white man, aged 78, admitted to the hospital on July 5, 1929, gave a history of distress of an ulcerous character of at least three years' duration. He said that on the morning of entrance, while riding in an automobile before breakfast, he was seized by an intense, knotlike, epigastric pain which within five minutes became almost intolerable. He was rushed to the nearest physician. When he reached the hospital about six hours later, the pain had been relieved. There was moderate tenderness and rigidity in the upper right quadrant of the abdomen. On Sippy management, the patient developed a progressive pyloric obstruction which necessitated surgical intervention. Laparotomy, performed on August 5, showed the duodenum covered by dense adhesions. An attempt to separate these resulted in the exposure of a defect located in the center of an indurated area, apparently a calloused duodenal ulcer.

GROUP 3: ROENTGENOLOGIC EVIDENCE OF PERFORATION (SPONTANEOUS PNEUMOPERITONEUM)

Although I had been led to believe from observations at the operating table that spontaneous recovery was not as rare as generally believed, it was not until I became acquainted with fluoroscopic observations in cases of acute upper abdominal pain that it became apparent that recovery from free perforation without operation was not at all uncommon. In a certain number of patients in whom spontaneous pneumoperitoneum was found, it was observed that at the time of entrance the severe initial symptoms had abated and the patients were no longer

seriously ill. A number of these persons entered for diagnosis or to convalesce, and although urged, refused to submit to operation. They apparently exercised good judgment, as they made speedy and complete recoveries. It soon became apparent that spontaneous closure of the perforation had occurred in some of these cases, and at the time of admission operation was no longer indicated.

In a search through the literature dealing with pneumoperitoneum following perforated peptic ulcer, several cases are found in which spontaneous recovery occurred (Assmann,[15] Ayerza and co-workers,[16] Copher,[17] Kellogg,[11] Kudlek,[18] du Pasquier,[12] Popper,[19] Schottmüller,[20] Wieland[21]). In a majority of these cases the frank admission is made that ruptured ulcer was not suspected until the roentgen examination disclosed accidentally the presence of free air. In some, operation was performed only to reveal that the perforation had been securely closed spontaneously. The case of Martin,[22] which presented conflicting abdominal and pulmonary signs, is interesting. Roentgenograms taken with the idea of demonstrating pneumonia showed what was interpreted by the roentgenologist, LeWald, to be free air in the peritoneal cavity. An ulcer was subsequently demonstrated.

CASE 11.—T. O., a white man, aged 68, admitted to the hospital on April 4, 1928, said that two weeks prior he experienced sharp, shooting pain in the upper part of the abdomen. The sharp pain became replaced by a constant soreness which was present at the time of entrance. He had perspired freely the previous night, and had had one chill the morning of admission. The temperature on entrance was 102 F. There was a history of intermittent attacks of mild epigastric distress characteristic of ulcer. A clinical diagnosis of subphrenic abscess was made. Roentgen examination showed a fluid level beneath the right dome of the diaphragm. With the barium sulphate meal, the duodenal bulb was seen to be defective. Subsequent roentgen examinations showed a gradual absorption of both the fluid and the air. The patient was discharged on May 28, apparently fully recovered.

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15. Assmann, H.: Klinische Roentgendiagnostik der inneren Erkrankungen, ed. 3, Leipzig, 1924, pp. 715-718.

16. Ayerza, L.; Espinola, R., and y Squirru, C. M.: Neumoperitoneo espontaneo, por fisuración de una úlcera del duodeno, Semana méd. **34**:1657, 1927.

17. Copher, G. H.: Demonstration of Spontaneous Pneumoperitoneum by the Roentgen Ray (An Aid in the Diagnosis of Acute Perforating Peptic Ulcer), J. A. M. A. **82**:781 (March 8) 1924.

18. Kudlek, F.: Zur Diagnose des durchgebrochenen Magengeschwürs, Zentralbl. f. Chir. **56**:1293, 1929.

19. Popper, H.: Die Diagnose der Darmperforation mit Hilfe der Röntgendurchleuchtung, Deutsche med. Wchnschr. **49**:1034, 1915.

20. Schottmüller, H.: Pneumothorax subphrenicus Infolge Ulcus ventriculi perforatum, Deutsche med. Wchnschr. **47**:892, 1921.

21. Wieland, W.: Ein röntgenologisches Phänomen bei perforiertem Magengeschwür, München. med. Wchnschr. **62**:537, 1915.

22. Martin, W.: Subacute Duodenal Perforation, Ann. Surg. **65**:773, 1917.

CASE 12.—J. N., a robust white man, aged 71, entered the hospital on Feb. 12, 1929, and related that he had suffered periodically from an ulcerous type of distress since the age of 21. Ten days prior to entrance, he experienced a sharp pain in the upper abdominal region described as resembling the thrust of a dagger. The pain continued to be severe for twelve hours in spite of medication. Vomiting occurred repeatedly. Hiccup began fifteen minutes after the onset of the pain, and was the presenting complaint at the time of admission. Physically, a palpable and audible rub could be detected over the lower right costal region. There was

Fig. 3 (case 14).—Pneumoperitoneum from ruptured peptic ulcer which occurred seven days prior to the time the roentgenogram was taken. The gas has accumulated beneath both domes of the diaphragm. Operation was not performed.

a shifting zone of tympany over the normal area of liver dulness. Physical signs of basal compression of the right lung and downward displacement of the liver were obtained. A diagnosis of pneumoperitoneum following perforated ulcer was made. The presence of air was subsequently demonstrated fluoroscopically and a defect of the duodenal bulb visualized in barium studies. The patient was discharged free from symptoms after roentgen examination showed an absence of free intraperitoneal gas.

Case 13.—T. M., a strapping young white man, aged 24, admitted to the hospital on March 12, 1929, said that five hours previously he was suddenly seized by a most atrocious pain which caused him to double up and roll about. He was given two hypodermic injections by a physician with only partial relief until the time of entrance. There was a history of intermittent attacks of ulcer pain occurring over a period of a year, recently aggravated and associated with an

Fig. 4 (case 14).—Roentgenogram taken four days after figure 3 and eleven days after perforation. The free air has been completely absorbed.

upward pressure. The symptoms and signs on admission were those of a mild peritonitis localized to the right upper quadrant. The general condition of the patient was excellent. A diagnosis of perforated ulcer with trifling leakage was made. Fluoroscopic examination demonstrated a small intraperitoneal air bubble. Spontaneous improvement was rapid. Examination after the ingestion of a barium meal on March 22 showed a universally deformed bulb. The patient was discharged free from symptoms.

CASE 14.—G. B., a colored man, aged 45, who had suffered from epigastric distress for twenty-five years, was admitted to the hospital on May 8, 1929, three days after the onset of excruciating abdominal pain. The intense initial pain subsided during the first twenty-four hours but recurred on the third day of illness. The physical signs at entrance were those of more or less diffuse peritonitis, pneumoperitoneum and bilateral compression of the bases of both lungs. A ruptured peptic ulcer was diagnosed. On May 9, the roentgen examination disclosed the presence of gas under both domes of the diaphragm. A series of subsequent roentgen examinations demonstrated a gradual spontaneous disappearance of the air (figs. 3 and 4). On May 25, a roentgen study with barium revealed a penetrating ulcer on the lesser curvature of the duodenum. The patient left the hospital fully recovered.

CASE 15.—J. S., a tall, slender, white youth, aged 20, was admitted to the hospital on July 4, 1929, with the following history: Since the age of 12 he had suffered from periodic epigastric distress of a mild nature. Three days prior to his acute illness, his previous distress became notably aggravated. On July 1, while sitting, he suddenly felt himself "tied in a knot." The severe pain of onset was transformed to a dull ache following hypodermic injections. Vomiting occurred with each attempt at ingestion. The clinical picture at entrance was that of a diffuse peritonitis with high grade meteorism. Although the diagnosis of a perforated ulcer was made clinically, surgical intervention was deemed inadvisable at that time, which was the fourth day of the acute illness. A roentgenogram made on July 5 showed free air beneath both domes of the diaphragm, considerable gas in the colon and a limited quantity in the small intestine (fig. 5). The evidences of infection gradually subsided spontaneously. By July 12, the free gas was practically entirely absorbed but the splenic flexure remained distended (fig. 6). The patient was ambulatory on the sixteenth and fully recovered on the twenty-third day following the onset of the perforation.

GROUP 4: CLINICAL EVIDENCE OF PERFORATION WITH ROENTGEN INDICATIONS OF ULCER

This group comprises those cases in which convincing testimony is lacking as direct evidence of a perforation either operative or roentgenologic is wanting. There is in each case a history of chronic ulcer distress, usually prodromes of perforation, and those symptoms and signs which characterize a perforative peritonitis. There is also evidence of ulcer or ulcer deformity in the barium meal study made an interval after the assumed perforation occurred. The justification for considering these cases as examples of spontaneous recovery is that clinically they differ in no essential way from those cases corroborated by operation or by the finding of a pneumoperitoneum.

In connection with this group of cases, it is interesting to analyze the report of Kudlek,[18] who aside from Vaughan and Brams [23] and Vaughan and myself [24] appears to be the only one who has published

23. Vaughan, R. T., and Brams, W. A.: Roentgen Ray in the Diagnosis of Perforated Peptic Ulcer, Surg. Gynec. Obst. **50**:10, 1930.

24. Vaughan, R. T., and Singer, H. A.: The Value of Radiology in the Diagnosis of Perforated Peptic Ulcer, Surg. Gynec. Obst. **49**:593, 1929.

roentgen observations on a large series of perforated ulcers. Kudlek stated that in twenty-four cases of ruptured ulcer examined roentgenologically twenty showed the presence of free air. In two of the four cases lacking pneumoperitoneum, laparotomy was immediately

Fig. 5 (case 15).—Roentgenogram taken five days after perforation. There is free air beneath both domes of the diaphragm and considerable gas in the splenic flexure. No operation.

resorted to, and in each case a perforation covered by omental fat was found. In the other two cases, operation was not performed on account of the relative mildness of the symptoms. Although both roentgen and operative confirmation of a perforation is lacking, Kudlek made no attempt to justify or prove the correctness of his diagnosis. He appar-

ently takes for granted that the reader concedes him the ability which he feels he possesses to recognize even the less typical cases because of his experience with similar cases checked by operation or by roentgenograms.

Fig. 6 (case 15).—Appearance of the x-ray film seven days after figure 5 was taken and twelve days after perforation. The free air has been almost completely absorbed. The splenic flexure remains distended by gas.

Particular care has been exercised to exclude those cases in which the severe pain is not due to perforation but to penetration of an ulcer into an adjacent structure. Here, as a rule, the pain is relieved by emptying the stomach or by the ingestion of large doses of alkali. Furthermore, the symptoms and signs of peritonitis are absent or at

least indefinite. In every case in this group, other causes of acute upper abdominal pain besides ulcer were considered in the diagnosis, and where indicated appropriate methods of examination were instituted.

Case 16.—J. B., a white man, aged 31, admitted to the hospital on Jan. 19, 1929, had noted occasional heart-burn for many years. For four days prior to entrance, shooting pain appeared in the right upper part of the abdomen radiating to the chest. At 10 a. m. on the day of admission, the patient was suddenly stricken with severe epigastric pain which soon became generalized. A hypodermic injection administered by a private physician relieved the patient of the intense suffering, although pain on deep respiration persisted. When admitted ten hours after onset, the patient presented a tender, diffusely rigid and retracted abdomen. The peristaltic sounds were diminished. Twenty-four hours after onset, the physical signs of peritonitis were limited to the right upper quadrant. Thirty-six hours after presumed perforation, the patient was ambulatory and desired to be discharged. There was slight residual tenderness at that time. Barium meal studies undertaken on January 25 disclosed a deformed bulb. Ulcer distress occurred during a four day period early in February. By means of alkalis and restriction of diet, the patient was rendered free from symptoms.

Case 17.—C. O., a white man, aged 35, was admitted to the hospital on Jan. 19, 1929, with the statement that six hours prior he experienced epigastric pain of such extreme intensity that he was forced to writhe on the floor. Within half an hour after onset, a physician was called who administered a hypodermic injection which failed to afford relief. There was an antecedent history of melena and periodic attacks of chronic ulcer distress, the last attack appearing in aggravated form three days before the onset of acute pain. On entrance, there were physical evidences of peritonitis localized to the right hypochondrium and to the region of McBurney's point. The temperature was 100 F. The pain continued to be severe for twenty-four hours but disappeared five days after admission. The last rise in temperature (99.2 F.) occurred the following day. On February 8, with the aid of a barium meal, a deformed duodenal bulb was demonstrated. Except for heart-burn precipitated by dietary indiscretions, the patient became free from symptoms.

Case 18.—G. M., a heavy-set, somewhat obese white man, aged 43, was admitted to the hospital on Jan. 23, 1929, with a history of postprandial upper abdominal pain of one month's duration. Gallbladder disease had been diagnosed. Three days before admission, he was suddenly attacked by an excruciating pain in the right hypochondrium which caused him to double up and beads of perspiration to appear and rendered his abdomen as "hard as a board." During the first twenty-four hours, even morphine failed to allay the suffering. When the patient was admitted the area over the right side of the abdomen was quite tender and moderately rigid. The temperature was 100.4 F. During the period of observation, right hypochondriac pain of a relatively mild type followed the ingestion of heavier foods. Aspiration at the height of the pain showed consistently the presence of an adequate acidity. There was practically immediate relief from aspiration and from alkalis used for test purposes. Examination of the stools while the patient was on a meat-free diet gave a persistently positive Weber reaction. Roentgen examination revealed a penetrating ulcer of the stomach. The Graham-Cole test showed a gallbladder of normal contour with no evidence of stones. The emptying time was normal. On Sippy management, all abdominal symptoms vanished.

CASE 19.—L. K., a tall, thin, white man, aged 25, was admitted to the hospital on July 21, 1929, with exquisite tenderness and clearcut rigidity in the epigastric and right hypochondriac regions. Gallbladder disease was originally diagnosed. Pertinent questions yielded the information that the patient had suffered from an ulcer syndrome which became particularly troublesome two days prior to entrance. On the day of admission, three and a half hours after a meal of cabbage and ham with vinegar, the patient experienced an atrocious epigastric pain which caused him to double up and to squirm about in bed. A private physician advised hospitalization. The patient was admitted four hours after the onset of severe pain. Several injections of morphine were required during the first forty-eight hours. The highest recorded temperature was 100.2 F. For a time, the act of micturition was associated with pain. On July 24, all the symptoms had disappeared and regular Sippy treatment for ulcer was instituted. Roentgen examination showed a general deformity of the bulb. The Graham-Cole test led to normal visualization of the gallbladder. The patient was discharged feeling entirely well.

CASE 20.—C. H., a white man, aged 70, entered the Cook County Hospital for a second time on Sept. 29, 1929. From the record of his first admission, it was learned that he was operated on for a perforated duodenal ulcer on Jan. 25, 1925. The hole was sutured, and a posterior gastro-enterostomy was performed. Following recovery from the operation, distress appeared only after dietary indiscretions. On Sept. 26, 1929, while on a streetcar, the patient was seized without warning by an extremely agonizing pain which caused him to scream and to fall from his seat. He was taken home in an automobile and treated by a private physician. The patient said that the abdomen was as "hard as stone." After twenty-four hours, the severe pain began to subside. Except for slight tenderness in the epigastrium and on the left side of the upper part of the abdomen, the results of the physical examination were negative. Roentgenographically, there was observed at the gastrojejunal stoma a filling defect, which disappeared after two weeks of ulcer management. The patient was discharged fully recovered presumably from a perforated gastrojejunal ulcer.

COMMENT

The general view with regard to the uniformity of the clinical course and the ease of diagnosis of ulcer perforations is summed up in the statement, "Perforation of the stomach into the general abdominal cavity is a catastrophe so sudden, so rapid and definite in its progress that it is generally recognized without difficulty." From a study of the foregoing case reports, however, one does not gain this impression. In the first place, the course of the disease appears quite variable and by no means uniformly progressive. Many of the cases indicate that following the initial severe manifestations of onset, instead of progression there is more or less rapid subsidence of symptoms and recovery. These are cases in which early closure of the perforation occurs and in which the amount of leakage from the stomach or duodenum is limited. The mildness of the clinical manifestations following onset led Vaughan [25] and myself to choose the term "formes frustes" with

25. Singer, H. A., and Vaughan, R. T.: The "Formes Frustes" Type of Perforated Peptic Ulcer, Surg. Gynec. Obst. **50**:10, 1930.

which to characterize these cases. In the second place, the recognition of perforated ulcer is not always a simple matter when all types are considered. Most of the foregoing cases were not correctly diagnosed by the original examiners. Moynihan [26] confessed that in eighteen of forty-nine cases which proved to be perforated ulcers he made a right lower quadrant appendical incision. Difficulty in diagnosis is encountered, especially in the formes frustes cases, which generally result in recovery without operation.

Only those cases which furnished evidence sufficient to satisfy the more skeptical were included in this report as instances of spontaneous recovery from perforated peptic ulcer. In addition to these forty cases, there were a number of others encountered during the course of the study in which perforation might be suspected. Noteworthy among these additional cases is a class in which the clinical picture of perforation is typical but in which operation is not performed, free air is lacking and subsequent barium studies fail to demonstrate indications of ulcer. The essential difference between this class and group 4 is the absence of roentgenologically demonstrable ulcers in the former. The class of cases in which perforation is followed by intra-abdominal suppuration which requires surgical intervention at some time cannot be rightly listed in the category of recovery without operation. Where drainage of a subphrenic or perigastric abscess is not required, as in case 11, one can justifiably speak of a spontaneous recovery.

The importance of the history can hardly be sufficiently emphasized. Unless the patient is seen early, with few exceptions, the diagnosis cannot be made without an adequate history. Even if the patient is observed within a limited period after onset, unless a satisfactory anamnesis is obtained it is difficult to arrive at a correct diagnosis. It is often necessary to suspect the presence of a perforation in order to choose the questions which yield a pertinent history. As a matter of fact, in more than a majority of spontaneous recoveries in this series the patient's story as recorded by the intern bore little resemblance to the characteristic history obtained after the diagnosis of perforated ulcer was entertained.

The mistake is often made of listing categorically the individual symptoms of which the patient complains and elaborating on the characteristics of each one. What is most essential for the diagnosis of acute perforation is a minute to minute chronological description of the onset and the subsequent few hours. In eliciting the mode of onset and early course, it is of extreme importance to have the patient narrate not only what he felt but also what action he took. For

26. Moynihan, B.: Abdominal Operations, ed. 4, Philadelphia, W. B. Saunders Company, 1926, vol. 1, p. 234.

instance, caeteris paribus, if a patient said that he experienced "an extremely agonizing and most intolerable" pain but nevertheless completed his day's work and sought no measures for relief, the diagnosis of perforation is less likely than when he asserts that he felt merely a "hard" pain, ceased work instantaneously and summoned medical aid immediately. The reader may have been struck by what appeared to him unnecessary details in the recorded case histories regarding activities of patients just prior to and after onset. These seemingly irrelevant items, however, will be found to furnish the physician with far better material on which to base a conclusion than the patient's subjective description of his complaints.

The question naturally arises as to how frequently spontaneous recovery would ensue if all patients with perforated ulcers were treated without surgical measures. The attempt to arrive at a trustworthy answer is beset with many difficulties. In the first place, since operation is performed in practically all cases of perforated ulcer which are recognized within the first twenty-four hours or so, it is difficult to estimate how many of these would have resulted in spontaneous closure if the surgeon had not intervened. In the second place, it is almost impossible to judge how many abortive or mild cases fail to come under medical observation, to say nothing of the number which are unrecognized when patients come under the observation of physicians. Thirdly, when the diagnosis is not checked by operation or by the presence of free air, there is always a possibility of error which must be taken into account.

In the absence of more accurate data, an estimate based on the foregoing study may be warranted at this time. During the period of observation, there were just as many cases of spontaneous recovery in patients treated in the hospital as there were perforations with continuous leakage. Based on this observation and on impression, it is estimated that the chances for recovery from perforation of a peptic ulcer into the free abdominal cavity is no less than 50 per cent; in other words, instead of constituting an almost invariably lethal complication of ulcer, perforation without operation is followed by recovery in at least one half of the total number of cases.

Because the statement is made that spontaneous recovery frequently occurs, it should not be assumed that conservative management is recommended. The possible bearing which the incidence of recovery without laparotomy has on present methods of treatment is not considered in this article. The object of the paper is merely to correct what appears to be a general misconception in regard to the outcome of perforations that are not handled surgically, and to throw light on a number of what were hitherto diagnostic problems and obscure phenomena.

SUMMARY

It has been almost universally agreed that when a peptic ulcer perforates into the free abdominal cavity the outcome is practically always fatal. This view has been so deeply impressed on the minds of the medical profession that when a patient recovers from a perforated ulcer it is usually thought that the rupture occurred into a preformed sac. The conception of perforation into a walled-off sac in cases of spontaneous recovery is contradicted by the presence fluoroscopically of freely movable intraperitoneal gas and by the absence of antecedent adhesions in cases in which laparotomy is performed. The adhesions encountered follow rather than precede the actual rupture. In other words, recovery from perforated ulcer without operation is conditioned not by preformed adhesions but by the sealing, plugging or covering of the hole after rupture into the free peritoneal cavity has already occurred.

Within a period of eighteen months, forty cases of spontaneous recovery from perforated ulcer have been collected from the medical and surgical wards in the Cook County Hospital. These cases can be conveniently divided according to the nature of the evidence of perforation into four groups: (1) cases in which operation undertaken shortly after the symptoms and signs of perforation appear show the fresh rupture; (2) cases with an antecedent history of chronic ulcer and of symptoms of perforation in which, after a lapse of time, adhesions presumably due to a perforated ulcer are demonstrated; (3) cases in which a history of ulcer and symptoms and signs of perforative peritonitis are associated with the presence of spontaneous pneumoperitoneum; (4) cases in which there is a history of chronic ulcer, symptoms and signs of a perforation and the presence in a barium study undertaken after a safe interval, of an ulcer deformity. Twenty representative case reports, five from each group, chosen to illustrate the most diverse types, are described in some detail.

The general belief that practically all cases of perforated peptic ulcer pursue a typical, progressive course is not borne out by a review of the case reports. Following the symptoms of onset, the clinical manifestations in many cases rapidly subside, and complete recovery ensues within from one to several days. These are "formes frustes" cases in which limited leakage occurs because the hole becomes spontaneously closed shortly after rupture takes place.

The universal statement that perforation of a peptic ulcer into the free abdominal cavity is readily recognized is also at variance with the impression gained by reading the details of the cases herein reported. In typical cases, the diagnosis is more or less obvious. How-

ever, in the mild and abortive types and in cases seen after the symptoms of onset have subsided, an incorrect diagnosis is generally made in a majority of instances.

The important points in the detection of many of the cases of spontaneous recovery are: (1) the knowledge that their occurrence is not uncommon, (2) a thorough acquaintance with the manifestations of the less typical perforations and (3) a careful and detailed minute to minute history. The history includes not only the subjective complaints of the patient, but also his actions and reactions in response to these symptoms.

Although accurate statistics cannot be offered on account of the inherent difficulties that stand in the way of a correct analysis, it is believed that spontaneous recovery occurs far more frequently than has hitherto been supposed. It is estimated that in a large series of cases of perforated ulcer in which surgical closure is not performed at least 50 per cent will recover.

The observation that spontaneous recovery from perforated peptic ulcer is a common occurrence is offered as a statement of fact which may aid in diagnosis and serve to elucidate a number of obscure clinical problems and statistical paradoxes. No conclusions are drawn in the article regarding the bearing which this observation might have on the present methods of treatment for perforated ulcer. No statement is made which contradicts the current belief that in general perforated ulcer constitutes a surgical emergency.

THROMBO-ANGIITIS OBLITERANS (BUERGER)

IV. REDUCTION OF BLOOD VOLUME *

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The high hemoglobin percentage and increased viscosity [1] that have been observed in patients with thrombo-angiitis obliterans for many years suggested the probability that in this disease there was concentration of the blood. Studies of blood volume begun several years ago by one of us tended to confirm this supposition, but the number of cases available for study at that time was too few to permit a definite conclusion to be drawn. The large number of patients with thrombo-angiitis obliterans who have been drawn to the special clinic established for this disease in the outpatient department of Mount Sinai Hospital has made available the clinical material for a more comprehensive study. From the data collected certain conclusions can now be drawn. This paper will deal only with the question of the amount of total blood and plasma in this disease.

TECHNIC

The dye method for determining the blood volume was used.[2] Ten cubic centimeters of blood was withdrawn; through the same needle 10 cc. of 1 per cent solution of congo red or vital red was injected. The patient was exercised to get as complete a distribution of the dye as possible. At the end of four minutes, 10 cc. of blood was withdrawn from the vein of the opposite arm. The two specimens were centrifugated at high speed (3,000 revolutions per minute) in calibrated, corked, centrifuge tubes for one hour. The exact level of cells and plasma was noted, and this was used as the hematocrit reading. The average of the two hematocrit readings was taken. The supernatant plasma was drawn off with a bulb pipet and put into clean test tubes.

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* From the Out-Patient Department and the Laboratories of the Mount Sinai Hospital.

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1. Mayesima, T.: Klinische und experimentelle Untersuchungen über die Viskosität des Blutes, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **24**:413, 1912.

2. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547 (Oct.) 1915.

The standard in each case was prepared by the dilution of 5 cc. of the same dye used for the patient with 500 cc. of distilled water in a volumetric flask. The same needle and syringe that were used for the injection of the dye into the circulation of the patient were used in this procedure in order to avoid any error due to different calibration of the syringe. The standard then had a dilution of dye equivalent to 1 cc. in 100, or 10 cc. in 1,000.

The dilution of dye in the dyed plasma was determined in a Meyer's colorimeter. Into one tube 0.5 cc. of standard solution and 0.5 cc. of normal plasma were added. Into the other tube 0.5 cc. of dyed plasma was added to 0.5 cc. of distilled water. The colors were compared. The standard was diluted until the colors matched, a solution of equal parts of normal plasma and distilled water being used as a diluent. The dilution was done with a graduated pipet, each cubic centimeter or fraction thereof being carefully noted. The original standard had a dilution equivalent to 10 cc. of dye in 1,000 cc. of solution. As used in the colorimeter, the dilution is doubled, or 10 cc. in 2,000 cc. of solution. For each cubic centimeter of diluent added, the dilution of the dye is increased by 2,000 cc. When the colors matched and the dilution was determined, the plasma volume was found by dividing the results in half.

The total blood volume was determined by the use of the hematocrit and the following ratio:

$$\frac{\text{Per Cent of Plasma}}{100\%} :: \frac{\text{Volume of Plasma}}{\times \text{ (total volume)}}$$

The following is an illustration of the determination of the total blood volume:

1.2 cc. of diluent used to bring standard color up to unknown.
The dilution was raised from 1/2,000 to 1/4,400.
Plasma volume was $\frac{4{,}400}{2} = 2{,}200$ cc.

The hematocrit was 45 per cent cells and 55 per cent plasma, therefore

$$\frac{55\ \%}{100\ \%} = \frac{2{,}200\text{ cc.}}{\times}$$

$$55 \times = 220{,}000 \qquad \times = 4{,}000 \text{ cc.}$$

Total blood volume was 4,000 cc.

The volume of the blood and plasma per kilogram of weight of the patient was readily estimated. The greatest care was used to make the technic uniform and as faultless as possible. Determinations were made in the early morning on a fasting stomach. To avoid hemolysis, syringes, needles and graduated centrifuge tubes were washed in physiologic solution of sodium chloride before being used. If infiltration of dye outside the patient's vein took place, the test was at once abandoned. The needle and syringe were fitted perfectly so that no dye was lost at the time of injection. Patients were exercised to insure a proper distribution of dye in the body. To prevent coagulation of the blood, 0.1 cc. of a 20 per cent solution of potassium oxalate was added to the graduated centrifuge tubes. This is strong enough to prevent clotting. The blood and oxalate were mixed thoroughly but carefully by inverting the tubes twice, the thumb being held over the opening. While centrifugation was taking place, the test tubes were corked to prevent evaporation. The colorimeter tubes were cleaned with alcohol and ether and thoroughly dried. The solution of congo or vital red was prepared by dissolving the powdered dye in triply distilled water. The solution was boiled and filtered twice and sealed in glass ampules which were then sterilized in the autoclave. As the technic improved with experience, several of the earliest deter-

minations were repeated, and the second result was used. When it was impossible to recall the patient, the earlier tests were discarded. When repeated, we used a different dye so as to prevent the nonspecific immunity reaction to the original dye which some workers claim will alter the final result.[3]

MATERIAL STUDIED

The cases studied are divided into groups according to the following classifications:

Group I.—Patients with typical cases of thrombo-angiitis obliterans, untreated, who are still smoking. The onset of symptoms occurred before the age of 45; clearcut physical signs are present.

Group II.—Similar to group I, but the patients have been treated by intravenous injections of hypertonic sodium chloride. Most of the patients have stopped smoking.

Group III.—Borderline cases of thrombo-angiitis obliterans. The onset is between the ages of 45 and 50. The involvement is much more extensive in one lower extremity. There is no history of diabetes. No calcification is found on roentgen examination.

Group IV.—Patients temporarily classed as having thrombo-angiitis obliterans, but the symptoms and physical signs are not typical. Early onset and usually mild involvement occur.

Group V.—Atherosclerosis. The onset occurs after 50; the involvement is about equal in both lower extremities; calcifications of vessels are seen on roentgen examination. There is a history of diabetes in some cases.

Group VI.—Normal persons used for control; patients with no evident vascular disease.

RESULTS

Study of the data presented reveals a striking reduction of the blood volume in the sixty-nine typical cases of thrombo-angiitis obliterans represented by the first two groups. As might be expected, the most striking figures are found in the group of untreated patients. Here the average blood volume per kilogram is 64.3 cc., a reduction of 22.3 per cent from our normal average. The treated patients also show a similarly reduced volume, which is slightly less than that for the untreated group. It should be borne in mind that all patients who stop smoking and receive treatment gain weight. Usually the gain is from 15 to 30 pounds (6.8 to 13.6 Kg.). This would tend to make the blood volume per kilogram less, unless an actual increase in the blood volume took place. The fact that the average volume per kilogram in this group is 65.9 cc., which is somewhat higher than that for the untreated group, may be interpreted as one of the effects of treatment.

It was noted by Keith, Rowntree and Geraghty,[2] and also by us, that in normal persons the blood volume per kilogram tends to diminish

3. Lindhard, J.: Dye Method for Determining the Blood Volume in Man, Am. J. Physiol. **77**:669, 1926.

TABLE 1.—*Typical Thrombo-Angiitis Obliterans (Untreated)*

Name	Age	Years of Illness	Smoking	Amputation	Hemoglobin, per Cent	Red Blood Cell Count	Weight, Kg.	Total Blood Volume	Total Plasma Volume	Blood Volume per Kg.	Plasma Volume per Kg.	Cell, per Cent	Plasma, per Cent
H. R.	44	10½	+++	1	122	3,710	81.8	3,956	2,200	48.3	26.8	44.4	55.6
R. Z.	42	19	++++	2	105	4,400	62.2	3,107	1,750	49.9	28.0	44.9	55.1
M. G.	59	19	++++	2	140	4,990	70.0	3,600	1,800	50.9	25.4	50.0	50.0
L. E.	36	8	+++	1	116	6,310	76.8	4,142	2,125	51.8	27.6	48.7	51.3
I. R.	44	17	++++	2	120	4,410	67.2	3,571	2,000	53.1	30.0	44.0	56.0
I. R.	26	1	++	..	100	5,970	57.2	3,225	1,750	56.3	30.5	46.2	53.8
Dr. G.	32	..	+++	..	120	.....	85.5	4,592	2,600	58.5	30.4	47.5	52.5
H. G.	44	½	++++	..	80	4,440	58.1	3,420	2,100	58.8	37.8	38.6	61.4
S. S.	41	13	++	2+	105	5,970	64.5	3,809	2,000	59.0	31.0	47.5	52.5
S. W.	48	¼	+++	..	100	4,860	73.8	4,384	2,100	59.4	28.4	47.9	52.1
D. B.	39	½	++++	..	126	5,970	69.0	4,174	2,250	60.5	32.6	46.1	53.9
S. M.	53	18	+++	2	92	5,060	47.7	2,972	1,700	62.0	35.4	42.7	57.3
J. J.	37	9	++++	2	90	6,770	67.2	4,166	2,250	62.0	33.4	46.0	54.0
A. B.	36	6	++++	1	102	6,800	62.0	4,541	2,625	73.3	42.2	42.2	57.8
	37	7	+++	2	95	5,800	....	4,218	2,400	62.7	35.7	43.1	56.9
A. K.	47	16	++++	2	124	5,030	66.3	4,175	1,900	63.0	28.0	54.5	45.5
A. S.	45	8	+++	2	120	4,230	46.3	2,949	1,700	63.4	36.7	42.8	57.2
A. K.	60	15	+++	2	105	5,380	68.0	4,326	2,280	63.6	33.5	47.3	52.7
M. G.	40	8	++++	..	102	5,550	67.5	4,371	2,400	64.7	35.5	45.1	54.9
M. L.	37	5	++	1	92	5,040	55.0	3,682	2,125	65.0	36.9	42.3	57.7
S. M.	44	16	++++	..	105	6,130	71.5	4,665	2,500	65.2	36.9	46.4	53.6
S. D.	34	1½	+++	1	115	6,350	43.6	2,850	1,500	65.3	34.8	47.5	52.5
O. L.	24	4	+++	..	105	6,080	67.3	4,494	2,400	66.7	35.6	46.6	53.4
C. H.	40	2	++++	..	...	.....	66.5	4,545	2,500	68.3	37.5	45.0	55.0
J. K.	40	2	++++	..	104	4,500	95.9	6,660	3,500	68.8	36.6	46.9	53.1
J. E.	36	3	+++	..	100	5,020	70.0	4,830	2,700	69.0	38.5	44.1	55.9
W. M.	40	2	+++	1	98	4,270	70.0	4,849	2,900	69.2	41.4	40.2	59.8
S. F.	45	21	++++	2	120	5,960	55.0	4,047	2,200	73.5	40.0	45.4	54.6
M. E.	34	4	+++	..	100	5,400	57.0	4,280	2,500	75.0	43.8	41.7	58.3
B. Z.	45	13	+++	2+	122	7,770	42.0	3,925	2,100	93.4	50.0	46.5	53.5
S. S.	35	10	++	1	...	.....	46.3	4,409	2,500	95.2	54.0	43.3	56.7
Average										64.3	35.3		

TABLE 2.—*Typical Thrombo-Angiitis Obliterans (Treated)*

Name	Months of Treatment	Age	Years of Illness	Smoking	Amputation	Hemoglobin, per Cent	Red Blood Cell Count	Weight, Kg.	Total Blood Volume	Total Plasma Volume	Blood Volume per Kg.	Plasma Volume per Kg.	Cell, per Cent	Plasma, per Cent
C. de M.	11	42	1	++++	..	100	5,000	78.1	3,710	2,000	46.4	25.0	44.6	53.4
M. R.	36	50	7	+++	1	96	6,050	54.4	2,680	1,500	49.6	27.7	44.0	56.0
D. S.	3	40	12	++++	..	105	5,800	68.1	3,623	2,000	53.1	29.3	44.5	55.5
											64.4	34.4		
W. K.	23	33	3	+++	..	95	5,390	84.5	4,495	2,625	53.2	31.0	41.6	58.4
L. R.	36+	42	12	++++	..	108	5,900	71.0	3,800	1,900	53.5	27.8	50.0	50.0
W. S.	3	36	5½	++++	..	108	6,140	80.0	4,880	2,625	53.7	27.1	46.3	53.7
N. D.	34	38	4½	+	..	111	5,110	79.1	4 365	2,400	54.9	30.4	45.0	55.0
N. F.	36+	47	20	+++	2	102	5,580	73.1	3,657	2,125	54.9	29.0	41.9	58.1
A. S.	33	53	16	++	1	105	5,150	84.3	4,880	2,750	57.8	32.7	43.6	56.4
I. L.	29	37	4	++	..	95	5,290	79.0	4,565	2,670	58.1	33.0	43.4	56.6
I. B.	7	47	19	++++	1	102	4,930	72.7	5,942	3,500	60.8	36.1	40.9	59.1
M. G.	36+	36	9	++	1	100	4,800	67.0	4,108	2,200	61.3	32.8	46.7	53.3
W. N.	34	50	3	++++	..	125	5,440	68.0	4,200	2,100	61.7	30.8	50.0	50.0
M. K.	13	41	3	+++	1	105	6,080	83.0	5,137	2,800	61.8	33.8	45.5	54.5
H. D.	8	38	8	+++	1	105	5,100	59.5	3,833	2,300	63.8	38.3	40.0	60.0
P. R.	36+	31	7	++++	..	...	.....	74.5	4,639	2,700	62.2	36.2	41.8	58.2
D. L.	16	39	2	+	..	120	4,800	56.3	3,597	1,900	63.5	32.0	47.2	52.8
E. L.	16	36	3	++++	..	110	5,390	60.0	3,820	2,100	63.6	35.0	45.1	54.9
L. W.	36+	42	4½	+++	..	70	3,850	68.8	4,378	2,125	63.8	36.4	42.9	57.1
N. S.	4+	45	4	+++	..	135	5,790	66.2	4,572	2,360	65.6	36.2	49.7	50.3
F. A.	36+	38	9	+++	..	100	5,020	64.5	4,270	2,400	66.0	36.9	43.8	56.2
J. O.	½	31	4	+++	..	116	5,910	76.3	5,078	2,600	66.5	32.7	48.8	51.2
N. D.	16	43	16	++	1	95	5,280	71.8	4,795	2,700	66.7	37.6	43.7	56.3
V. N.	16	37	2	+++	..	110	5,000	64.3	4,296	2,200	66.8	34.2	48.8	51.2
S. Z.	18	42	2	++	..	104	6,050	89.3	6,000	3,300	67.2	36.9	45.0	55.0
A. R.	3	31	2½	+++	..	120	5,360	72.7	4,869	2,800	67.6	36.6	42.5	57.5
H. K.	10	34	1	++++	..	115	5,200	60.0	4,089	2,230	68.1	36.6	46.2	53.8
						105	4,020	60.0	4,431	2,300	73.8	38.3	48.1	51.9
A. F.	12	49	11	++	1	97	6,040	60.9	3,952	2,100	68.2	34.4	47.1	52.9
B. B.	7	30	6	++++	..	120	6,400	61.7	4,220	2,330	68.2	37.2	45.5	54.5
R. B.	36	53	19	++	..	90	5,780	91.3	6,306	3,500	69.0	38.3	44.5	55.5
H. E.	30	44	28	+	1	100	5,020	78.6	5,504	2,900	70.0	36.9	47.5	52.5
E. A.	27	41	8	+++	1	95	4,200	59.0	4,363	2,400	70.1	38.5	45.0	55.0
L. F.	24	31	4	++	..	115	5,500	68.2	4,800	2,800	70.3	38.6	47.9	52.1
D. L.	20	35	5	+++	1	116	6,020	69.5	5,513	2,900	71.0	37.7	47.4	52.6
S. W.	17	36	6	++	1	98	4,440	91.8	6,688	4,000	72.9	43.5	40.2	59.8
M. H.	18	43	½	+	..	105	5,020	65.4	5,045	2,800	77.1	42.8	44.5	55.5
						112	5,940	70.5	6,049	3,200	83.3	44.4	47.1	52.9
N. R.	21	43	14	++	..	120	5,120	58.6	4,635	2,350	79.0	40.0	49.3	50.7
W. K.	36+	44	3	+++	1	110	.....	61.0	6,143	3,600	100.7	59.0	41.4	58.6
P. E.	36+	40	17	+++	2	128	5,940	50.4	5,088	2,600	100.9	53.5	48.9	51.1
Average											65.9	36.4		

TABLE 3.—*Borderline Thrombo-Angiitis Obliterans*

Name	Months of Treatment	Age	Years of Illness	Smoking	Amputation	Hemoglobin, per Cent	Red Blood Cell Count	Weight, Kg.	Total Blood Volume	Total Plasma Volume	Blood Volume per Kg.	Plasma Volume per Kg.	Cell, per Cent	Plasma, per Cent
L. W.	3	50	¼	++++	..	125	5,150	75.0	4,664	2,500	62.1	33.3	46.4	53.6
M. S.	13	53	4	++++	..	105	5,270	65.0	4,545	2,500	65.0	38.4	45.0	55.0
L. K.	1	48	1	+++	..	...	.....	67.5	4,455	2,200	66.0	32.5	50.6	49.4
H. S.	5	47	3	++++	..	116	5,530	62.6	4,158	2,100	66.2	33.4	49.5	50.5
M. D.	7	56	7	++++	..	120	5,440	71.6	4,860	2,600	67.8	36.3	46.5	53.5
S. C.	5	49	4	+++	..	100	4,770	69.3	4,853	2,750	69.2	39.8	43.5	56.5
B. P.	1	54	1½	+++	..	140	4,230	78.1	5,630	2,600	72.1	33.3	52.6	47.4
D. G.	7	55	6	+++	1	112	5,420	61.3	4,570	2,550	74.5	41.3	44.2	55.8
B. M.	17	50	5	+++	..	95	4,670	70.0	5,463	2,950	78.0	42.1	46.0	54.0
L. J.	2	48	⅝	+++	..	98	4,520	61.5	4,846	2,800	78.8	45.5	41.6	58.4
J. S.	2	49	1½	+++	..	100	5,010	61.8	4,905	2,700	79.3	45.3	42.9	57.1
I. S.	0	45	1	++++	..	95	4,441	63.1	5,263	3,100	83.4	47.5	41.1	58.9
Average											71.8	39.0		

TABLE 4.—*Atypical Thrombo-Angiitis Obliterans*

Name	Months of Treatment	Age	Years of Illness	Smoking	Hemoglobin, per Cent	Red Blood Cell Count	Weight, Kg.	Total Blood Volume	Total Plasma Volume	Blood Volume per Kg.	Plasma Volume per Kg.	Cell, per Cent	Plasma, per Cent
E. M.	0	42	½	++++	116	5,900	86.3	5,416	2,925	63.3	33.8	46.0	54.0
T. C.	5	44	¼	+++	110	6,080	77.7	5,340	2,850	68.8	38.1	46.7	53.3
I. S.	5	38	3	++++	90	4,870	57.9	4,207	2,600	72.6	44.5	38.2	61.8
H. S.	5	40	3	+++	120	5,380	73.6	5,458	2,800	74.7	38.0	48.7	51.3
L. F.	1	33	¼	+	115	5,860	64.1	5,165	2,650	79.5	40.7	48.7	51.3
A. W.	0	44	3	+++	105	5,440	56.5	4,930	2,500	87.2	44.2	49.3	50.7
Average										74.3	39.9		

TABLE 5.—*Atherosclerosis*

Name	Months of Treatment	Age	Years of Illness	Smoking	Amputation	Hemoglobin, per Cent	Red Blood Cell Count	Weight, Kg.	Total Blood Volume	Total Plasma Volume	Blood Volume per Kg.	Plasma Volume per Kg.	Cell, per Cent	Plasma, per Cent
M. L.	21	56	5	++++	..	80	3,760	54.5	3,663	2,225	67.3	42.6	39.4	60.6
M. F.	28	51	4½	++++	..	102	4,580	75.4	5,370	2,900	71.2	39.5	46.0	54.0
P. A.	1	51	1½	++	..	116	4,370	76.1	5,936	3,200	78.0	42.0	46.1	53.9
H. McG.	18	55	2	++	..	104	4,720	68.0	5,400	2,914	79.0	42.0	46.0	54.0
A. R.*	1	71	?	+++	1	...	.....	64.0	5,087	2,900	79.5	45.3	43.0	57.0
M. C.	0	59	⅝	+++	..	102	5,280	75.9	6,078	3,100	79.9	40.7	49.0	51.0
B. S.*	0	42	?	?	..	...	.....	51.8	4,309	2,900	83.0	57.0	32.7	67.3
I. C.	3	55	9	+++	..	120	4,080	51.3	4,400	2,200	86.1	43.0	50.0	50.0
C. K.*	0	76	?	?	..	...	.....	51.0	5,374	2,800	94.6	49.3	47.9	52.1
Average											79.8	44.2		

* Diabetic patient.

TABLE 6.—*Controls*

Name	Age	Smoking	Weight, Kg.	Hemoglobin, per Cent	Red Blood Cell Count	Total Blood Volume	Total Plasma Volume	Blood Volume per Kg.	Plasma Volume per Kg.	Cell, per Cent	Plasma, per Cent	Illness
J. S.	34	..	70.9	...	.....	5,200	2,600	73.3	36.6	50.0	50.0	Ureteral calculus
S. S.	29	+	67.0	110	5,200	5,056	2,700	75.3	40.3	46.6	53.4	
L. A.	40	..	70.4	...	.....	5,309	3,000	75.9	42.6	43.5	56.5	Ureteral calculus
W. B.	52	++	68.9	...	.....	5,263	2,600	76.3	37.7	50.6	49.4	Hypertrophy of breast
J. D.	29	+++	80.0	...	.....	6,153	3,200	76.8	40.0	48.0	52.0	Cut hand
M. N.	42	..	68.1	...	.....	5,389	2,700	76.8	39.5	49.9	50.1	Rectal ulcer
M. K.	45	+	75.2	110	5,450	5,882	3,300	78.2	43.8	43.9	56.1	Varicose veins
S. F.	27	..	63.6	...	.....	5,008	2,800	78.5	43.7	44.1	55.9	
L.	48	..	63.6	...	.....	5,024	2,600	78.9	41.9	48.3	51.7	Gastric ulcer
Dr. S.	20	+	62.3	95	4,940	5,055	2,750	80.0	43.5	45.6	54.4	
O. N.	19	+	64.3	105	5,130	5,216	2,890	81.2	43.0	44.6	55.4	Skin infection
H. H.	18	..	72.3	...	.....	5,929	3,000	82.0	41.0	49.4	50.6	Pneumonia
S. G.	22	+++	65.0	119	6,260	5,500	2,800	84.6	43.0	49.1	50.9	Infected sebaceous cyst
S.	42	..	55.4	...	.....	4,715	2,600	85.1	46.0	44.8	55.2	Gastric ulcer
F. R.	41	..	74.5	...	.....	6,349	3,200	85.2	43.0	49.6	50.4	Cholecystitis
S. N.	23	+++	69.0	...	.....	5,906	3,400	86.7	49.1	43.3	56.7	Normal
A. K.	25	++++	74.5	...	.....	6,679	3,500	87.0	47.0	47.6	52.4	Normal
G.	39	..	67.2	...	.....	5,894	3,450	87.7	51.5	41.5	58.5	Gastric neurosis
J. H.	17	0	57.2	...	.....	5,156	2,800	90.0	48.0	45.7	54.3	Infected nail
A. F.	13	0	57.7	80	5,470	5,228	3,200	90.6	55.4	38.8	61.2	Ulcer of foot
A. L.	26	++	52.2	...	.....	4,938	2,800	94.6	53.7	43.5	56.5	Gastric symptoms
G.	44	..	59.1	...	.....	5,708	3,200	96.5	54.2	42.2	57.8	
Average								82.7	44.7			

as the weight increases. Study of our thrombo-angiitis obliterans cases shows a parallel tendency, even though the volume is already less (chart 1). Similar study of the influence of age on blood volume fails to show any changes due to this factor, either in normal persons [2] or in our group of patients with thrombo-angiitis obliterans (chart 2).

Of the group of sixty-nine cases classed as typical thrombo-angiitis obliterans, seven showed a blood volume of 75 cc. or more per kilogram. Retesting in some of these cases showed that error in technic was not responsible for these high figures. The conclusion must be drawn that about 10 per cent of cases do not show the typical reduction in blood volume. We have no explanation for this fact at the present time. If this 10 per cent is excluded, the average blood volume in the typical cases is much lower.

TABLE 7.—*Table of Averages*

Group	Number of Cases	Blood Volume per Kg.	Reduction from Normal, per Cent	Plasma Volume per Kg.	Reduction from Normal, per Cent
I. Thrombo-angiitis obliterans, typical, untreated	30	64.3	22.3	35.3	21.1
II. Thrombo-angiitis obliterans, typical, treated	39	65.9	20.4	36.4	19.6
III. Thrombo-angiitis obliterans, borderline	12	71.8	13.2	39.0	12.8
IV. Thrombo-angiitis obliterans, atypical	6	74.3	10.2	39.9	10.8
V. Atherosclerosis	9	79.8	3.6	44.2	1.2
VI. Controls (normal)	22	82.7	....	44.7	....

Group III includes patients with circulatory disease of the extremities whose symptoms began after the age of 45, but who otherwise present the characteristic features of thrombo-angiitis obliterans. They might therefore be classed as having a mild form of the disease, and it is interesting to note that the reduction in blood volume is also less striking. It is possible that owing to the slow development, compensation has taken place to a considerable extent.

In group IV, the figures for blood volume are nearly normal, 74.3 cc. per kilogram. This group of patients is included with those with thrombo-angiitis obliterans for the time being, but there is a reasonable doubt that they belong to the group. A variety of conditions may occasionally lead to some organic obstruction of the circulation, such as presenile atherosclerosis, arteritis associated with infectious diseases, thromboses resulting from trauma or other injury, etc. A few of these cases may represent mild forms of thrombo-angiitis obliterans.

Group V presents a series of cases of vascular occlusion due to another type of pathologic process, atherosclerosis. These cases were studied in order to determine whether the reduction of volume was caused by mere obliteration of the vascular area, which is present in atherosclerosis as it is in thrombo-angiitis obliterans. It is interesting

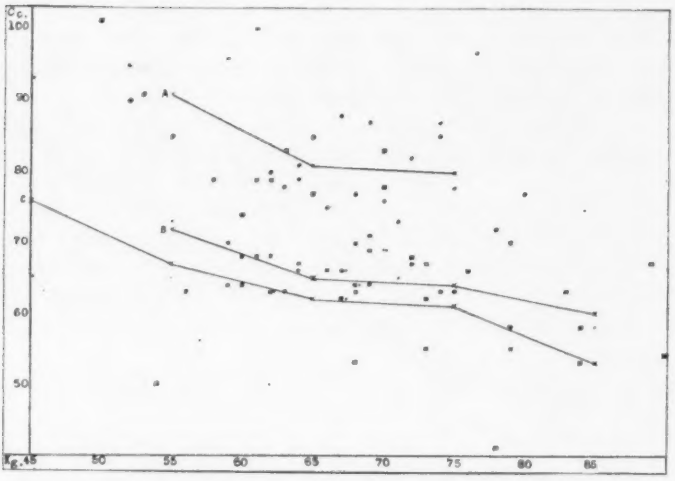

Chart 1.—Relation of weight to blood volume. *A* indicates the curve for normal persons; *B*, that for treated patients with thrombo-angiitis obliterans, and *C*, that for untreated patients with thrombo-angiitis obliterans.

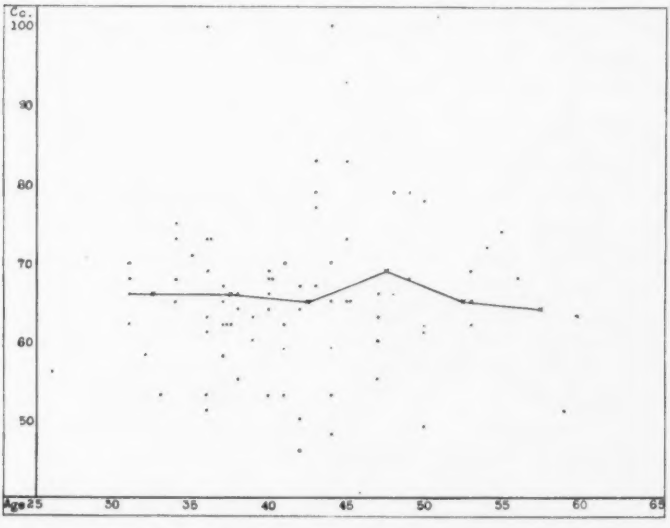

Chart 2.—Relation of age to blood volume (groups I, II and III).

to note that reduction of blood volume is not present in these cases. This fact would suggest that some factor which is part of the disease process in thrombo-angiitis obliterans is responsible for the reduction.

Finally, in group VI a series of controls establishes a normal average figure for the technic employed. This average corresponds with the figures obtained by other investigators for normal persons.[2]

It is noteworthy that in the cell-plasma ratio, as established by the hematocrit method, a slight tendency for a higher percentage of cells may be discerned. It is possible that the actual number of cells is nearly normal, and their apparently higher count is due to concentration in a smaller amount of plasma. Studies of the individual constituents of the plasma to determine their amount and relative proportions have been made and will be reported on later.

SUMMARY AND CONCLUSIONS

1. A study of blood volume by the dye method in eighty-seven cases of thrombo-angiitis obliterans, nine cases of atherosclerosis and twenty-two normal persons was made.

2. An average reduction of 21 per cent in blood volume was found in sixty-nine typical cases of thrombo-angiitis obliterans.

3. This fact suggests that a concentration of the blood is usually present in this disease.

THE CARDIAC OUTPUT IN HEART DISEASE

II. EFFECT OF EXERCISE ON THE CIRCULATION IN PATIENTS WITH CHRONIC RHEUMATIC VALVULAR DISEASE, SUBACUTE RHEUMATIC FEVER AND COMPLETE HEART BLOCK *

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Our object in this study was to determine the effect of exercise on the cardiac output of several patients with heart disease. These patients were studied first under basal conditions, and the results were reported in paper I.[1] The group consisted of three patients with chronic rheumatic valvular disease, one with subacute rheumatic fever, one with probable "chronic myocarditis" and two with complete heart block. In addition, control observations were made on four normal subjects, one of whom was obese.

The effect of graded exercise (by means of the stationary bicycle) on the output of the heart in normal subjects has been reported by Krogh and Lindhard,[1a] Means and Newburgh,[2] Boothby,[3] Collett and Liljestrand,[4] and Bock and his co-workers.[5] The earlier workers used the nitrous oxide method to determine the cardiac output, whereas Bock's observations were made with the modified "Haldane method." The latter procedure, as described by Bock, Dill and Talbott,[6] was used

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* From the Medical Clinic of the Peter Bent Brigham Hospital.

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5. Bock, A. V.; Vancaulaert, C.; Dill, D. B.; Fölling, A., and Hurxthal, L. M.: Studies in Muscular Activity: III. Dynamical Changes Occurring in Man at Work, J. Physiol. **66**:136, 1928.

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in our studies. In general, these authors have found that the cardiac output increases in direct proportion to the respiratory metabolism but that considerable variations exist in different persons at a given level of oxygen consumption.

Few observations have been reported on the output of the diseased heart during exercise. Means and Newburgh [2] studied the effect of exercise on the oxygen consumption and the cardiac output in a patient with double mitral and aortic disease. This patient had moderate cardiac enlargement but was able to do light work without discomfort. The reaction of this patient was similar to that of a normal subject until the amount of work exceeded 630 kilogram meters per minute; he then experienced considerable distress, whereas a normal subject could do work up to 1,040 kilogram meters per minute without difficulty. It is interesting to note that this patient complained more of general fatigue than of real dyspnea with the higher grades of exercise. Meakins, Dautrebande and Fetter [7] studied the cardiac output in three patients with mitral stenosis immediately after mild effort. The work was very light as the carbon dioxide excretion did not exceed 200 cc. a minute, while in our observations, with the lightest grade of work, the carbon dioxide excretion averaged between 700 and 800 cc. a minute. In their cases, the cardiac output increased from a resting level of from 3 to 4 liters a minute to about 5 liters a minute after exercise. The patients experienced symptoms out of all proportion to the work done.

Lundsgaard [8] studied two elderly patients with complete heart block. Both had previously been decompensated, and one had mitral insufficiency and auricular fibrillation. Directly following mild exercise, he found a marked increase in the coefficient of utilization (nitrous oxide method). The oxygen consumption was not measured, but from the high coefficients of utilization, he concluded that the minute circulation could not be increased appreciably. During exercise, both patients had moderate elevations in the ventricular rate (from 36 to 48 and from 40 to 46). Liljestrand and Zander [9] studied the effect of various grades of exercise on the cardiac output of a young patient with uncomplicated complete heart block. The ventricular rate increased from an average of 50 during rest to around 100 beats a minute during heavy exercise.

7. Meakins, J.; Dautrebande, L., and Fetter, W. J.: The Influence of Circulatory Disturbances on the Gaseous Exchange of the Blood: IV. The Blood Gases and the Circulation Rate in Cases of Mitral Stenosis, Heart **10**:153, 1923.

8. Lundsgaard, C.: Untersuchungen über das Minutevolumen des Herzen bei Menschen: III. Messungen an zwei Patienten mit totalem Herzblock, Deutsches Arch. f. klin. Med. **120**:481, 1916.

9. Liljestrand, G., and Zander, E.: Studies of the Work of the Heart During Rest and Muscular Activity in a Case of Uncomplicated Total Heart Block, Acta med. Scandinav. **66**:501, 1927.

The cardiac output responded normally to different grades of work, there being a minute output of 16 liters when the oxygen consumption was 1,500 cc. a minute. The stroke volume seemed to be limited at about 100 cc. No studies of the cardiac output under exercise are reported for patients with complete heart block in whom the ventricular rate did not increase with exertion.

PROCEDURE

Repeated observations were made in each subject, two standard grades of work being used. The exercise was obtained with the Krogh bicycle ergometer [10] which was well adapted for the repetition of a standard amount of work. A uniform rate of 36 revolutions of the sprocket per minute was used. Every subject was able to keep the down stroke of each pedal in time with a metronome adjusted at 72 beats a minute. Two different loads were applied by means of an electromagnet. These, with the uniform rate, amounted to work of 234 and 351 kilogram meters per minute respectively, and simulated riding a bicycle on level ground and up a slight slope at the rate of about nine miles an hour. Each subject had a preliminary practice period on the bicycle, in order to acquaint him with the procedure. All observations were made either two hours after breakfast or two hours after a light lunch. Following a resting period of ten minutes on the bicycle, exercise was begun. From seven to ten minutes was allowed for the establishment of a "steady state" before the cardiac output was determined.

The method used for measuring the cardiac output during exercise has been described by Bock, Dill and Talbott.[6] This is essentially the method of Field, Bock, Gildea and Lathrop [11] used in resting subjects (described in paper I), with two modifications. First, in collecting the alveolar air, the former group found that more accurate results are obtained by giving the command "blow" at the beginning of expiration instead of at the end, as is employed in resting subjects. This prevents piling up of carbon dioxide which would result in increased values. Second, in collecting the "virtual venous" sample of carbon dioxide (that which is in equilibrium with the carbon dioxide of the venous blood), the subject holds the oxygen-carbon dioxide mixture in his lungs instead of rebreathing into the bag. During the "holding period," the carbon dioxide of this mixture becomes in equilibrium with the carbon dioxide of the venous blood. The subject then expires forcibly and the sample is collected from a side arm before it reaches the rubber bag. A holding period of from nine to twelve seconds is necessary when the oxygen consumption ranges from 750 to 1,500 cc. a minute. In our studies, holding periods of ten seconds were used in every case, as the oxygen consumption averaged between 800 and 1,100 cc. a minute. A mixture of 91.5 per cent oxygen and 8.5 per cent carbon dioxide was used in the bag, as this was the approximate percentage of carbon dioxide that we found in the virtual venous samples during exercise. After the collection of each sample, from 12 to 15 cc. of carbon dioxide was added to the bag to make up for any loss sustained from dilution of the mixture with air in the dead space of the respiratory tract.

10. Krogh, A.: A Bicycle Ergometer and Respiration Apparatus for th Experimental Study of Muscular Work, Skandin. Arch. f. Physiol. **30**:375, 191

11. Field, J. H.; Bock, A. V.; Gildea, E. F., and Lathrop, F. L.: The Ra of the Circulation of the Blood in Normal Resting Individuals, J. Clin. Investigation **1**:65, 1924.

Four alveolar and four venous carbon dioxide samples were collected during each period of exercise according to this method. The expired air was collected in a 125 liter spirometer for two minute periods, once after the first alveolar and venous samples and again after the third. Taking the alveolar and venous carbon dioxide samples did not seem to affect the respiration or the metabolism, as spirometer periods taken just before and after these samples gave similar results. The calculations presented in table 1 show how the cardiac output was derived.

Heart rates were obtained every two to four minutes by palpation of the radial artery or by direct auscultation over the precordium, and blood pressures were recorded at the same intervals with a Tycos syphygmomanometer that was kept in place throughout the procedure. Respirations were counted by observing the

TABLE 1.—*Method of Calculating Cardiac Output (Case 4)*

No.	Alveolar Percentage of Carbon Dioxide, Mm. Hg	Venous Percentage of Carbon Dioxide, Mm. Hg	Arteriovenous Difference in Percentage of Carbon Dioxide, Mm. Hg
1	38.6	57.5	18.9
2	39.2	58.9	19.7
3	36.4	56.4	20.0
4	37.2	57.0	19.8

Average arteriovenous difference *19.6 mm.
Slope on dissociation curve..... 0.42
†Carbon dioxide transport, per cent by volume 8.03

Metabolism Period 1

Oxygen..... 17.12 per cent
Carbon dioxide..... 3.67 per cent

Respiratory quotient..... $\frac{3.64}{3.85} = 0.94$

Ventilation per minute..... 26,900 cc.
Oxygen consumption per minute.... 1,039 cc.
Carbon dioxide produced per minute 982 cc.

Metabolism period 2

Oxygen..... 17.18 per cent
Carbon dioxide..... 3.54 per cent

Respiratory quotient..... $\frac{3.51}{3.81} = 0.92$

Ventilation per minute..... 28,000 cc.
Oxygen consumption per minute.... 1,097 cc.
Carbon dioxide produced per minute 983 cc.

Calculation of Cardiac Output

Average carbon dioxide produced per minute..... 982.5 cc.
Carbon dioxide transport..... 8.03 per cent by volume

Cardiac output per minute..... $\frac{982.5 \times 100}{8.03} = 12,235$ cc.

* Normal standard dissociation curves, plotted at rest and during exercise (Bock, A. V.; Field, H., Jr., and Adair, G. S.: J. Biol. Chem. **59**: 353, 1924. Bock, A. V.; Dill, D. B.; Hurxthal, L. M.; Lawrence, J. S.; Coolidge, T. G.; Dailey, M. L., and Henderson, L. J.: Ibid. **73**: 749, 1927), were employed in these experiments. The determination of individual carbon dioxide dissociation curves was thought unnecessary since all our subjects had a normal amount of hemoglobin and there was no cause for an abnormal amount of fixed base. Furthermore, Meakins and others (Meakins, Dautrebande and Fetter, footnote 6) have found that carbon dioxide dissociation curves (on arterial blood by indirect observation) are normal in patients with mitral stenosis.

† The carbon dioxide transport is decreased by 0.2 per cent by volume because the arterial blood is only 95 per cent saturated.

opening and closing of the flutter valves on the inlet tube. The total period of exercise usually lasted from twenty to twenty-five minutes. The heart rate, blood pressure and respiration were then followed until a resting level was reached.

The so-called steady state as described by Bock and his associates[12] is illustrated in these studies by the relative similarity of observations made during a period of exercise. The arteriovenous carbon dioxide differences determined over an interval of from ten to fifteen minutes show even closer agreement than similar differences when taken at rest. Spirometer periods taken from five to

12. Bock, A. V.; Vancaulaert, C.; Dill, D. B.; Fölling, A., and Hurxthal, L. M.: Studies in Muscular Activity: IV. The "Steady State" and the Respiratory Quotient During Work, J. Physiol. **66**:162, 1928.

TABLE 2.—*Observations in Normal Subjects and in Patients with Heart Disease at Rest and During Exercise*

Date, 1929	Work, Kilogram-Meters per Minute	Pulse Rate	Blood Pressure: Systolic, Mm. Hg	Blood Pressure: Diastolic, Mm. Hg	Pulse Pressure	Respiration	Ventilation Liters per Minute	Oxygen Consumption per Minute, Cc.	Carbon Dioxide Expired per Minute, Cc.	Respiratory Quotient	Arteriovenous Difference in Percentage of Carbon Dioxide: Alveolar, Mm. Hg	Arteriovenous Difference in Percentage of Carbon Dioxide: Venous, Mm. Hg	Arteriovenous Difference in Percentage of Carbon Dioxide, % by Volume	Cardiac Output, Liters per Minute	Stroke Volume, Cc.	Comment
M. F., a man, aged 29; height, 177 cm.; weight, 63 Kg.; vital capacity, 5,200 cc.; normal																
Jan. 7, p.m.	Basal	63	120	78	42	12	5.8	250	199	0.80	40.5	50.4	4.09	4.9	77	
Feb. 14	Basal	60	114	80	34	13	6.0	260	201	0.78	41.0	50.5	4.2	4.7	78	
Feb. 1, p.m.	234	119	140	75	65	18	19.9	877	840	0.96	45.4	62.8	6.76	12.4	104	
Feb. 6, p.m.	234	108	135	75	60	17	19.1	808	767	0.95	43.0	60.6	6.83	11.2	104	Slight fatigue of legs
Feb. 21, a.m.	351	122	155	80	75	18	26.3	1,205	1,105	0.92	42.3	60.6	7.48	14.8	121	
S. L., a man, aged 38; height, 171.5 cm.; weight, 60.3 Kg.; vital capacity, 4,000 cc.; normal																
Feb. 6	Basal	59	108	68	40	12	4.8	195	157	0.82	41.4	51.7	4.27	3.7	65	
Feb. 18	Basal	53	110	68	42	9	4.4	210	153	0.73	40.1	49.6	4.00	3.8	72	
Feb. 9, p.m.	234	115	145	75	70	18	19.3	775	749	0.97	38.8	59.1	8.3	9.1	79	Moderate fatigue of legs
Feb. 16, p.m.	351	142	155	75	80	19	23.1	.....	1,006	....	41.9	62.4	8.0	12.6	89	Respiratory infection since last experiment
Mar. 2, p.m.	351	130	140	70	70	17	22.4	1,050	992	0.95	43.4	62.1	7.28	13.6	105	
E. H., a man, aged 27; height, 178 cm.; weight 74.2 Kg.; vital capacity, 5,300 cc.; normal																
Jan. 5	Basal	75	128	90	38	17	5.9	248	200	0.81	44.5	51.7	2.81	7.1	95	
Jan. 12	Basal	84	130	80	50	16	6.4	264	194	0.75	42.4	48.9	2.64	7.4	88	
Jan. 31, p.m.	234	109	150	80	70	23	18.4	783	714	0.92	44.3	58.9	5.6	12.7	117	
Feb. 4, p.m.	234	103	150	75	75	23	18.9	777	770	0.99	44.9	49.0	5.44	14.2	137	
Feb. 25, a.m.	351	129	155	78	77	23	22.8	980	964	0.98	44.2	61.4	6.68	14.4	120	Head cold for five days
R. K., a man, aged 29; height, 180 cm.; weight, 95 Kg.; vital capacity, 4,200 cc.; normal (obesity)																
Feb. 14	Basal	63	120	84	36	14	9.7	304	290	0.95	35.9	46.2	4.51	6.4	102	
Feb. 16	Basal	62	118	80	38	12	8.5	299	262	0.88	33.3	44.6	5.07	5.2	83	
Feb. 7, p.m.	234	92	140	85	55	19	22.4	1,250	910	0.73	41.2	56.2	6.11	14.9	162	
Feb. 13, a.m.	234	98	145	90	55	15	20.8	1,031	916	0.89	43.4	59.1	6.07	15.1	154	
Feb. 21, p.m.	351	106	160	100	60	9	18.9	1,240	1,053	0.85	41.1	61.7	8.43	12.5	119	
Feb. 26, p.m.	234	98	138	98	40	7	15.8	985	819	0.83	38.0	55.7	7.22	11.3	116	
Feb. 28, p.m.	351	107	155	95	60	6	16.9	1,230	1,042	0.85	42.9	63.1	8.08	12.9	120	

F. M., a man, aged 25; height, 178 cm.; weight, 72 Kg.; vital capacity, 5,200 cc.+; diagnosis, mitral insufficiency and stenosis

Average basal		79	125	86	39	15	6.4	274	220	0.80	39.4	48.4	3.84	5.7	72	
Feb. 20, a.m.	234	115	130	89	41	21	19.4	889	810	0.91	39.7	58.3	7.52	10.8	93	
Feb. 20, p.m.	351	121	138	82	56	18	24.5	1,245	1,138	0.91	43.5	63.3	7.72	14.8	122	

I. C., a boy, aged 17; height, 171 cm.; weight, 70.5 Kg.; vital capacity, 3,300 cc.; diagnosis, mitral insufficiency and stenosis and aortic insufficiency (advanced)

Average basal		67	140	30/0	110	13	5.6	269	208	0.77	39.6	52.1	5.23	4.0	59	
Feb. 9, p.m.	234	119	185	60/0	125	24	20.0	868	814	0.94	41.3	58.7	7.27	11.2	94	Marked fatigue, slight dyspnea

S. T., a boy, aged 16; height, 168 cm.; weight, 61 Kg.; vital capacity, 3,400 cc.; diagnosis, mitral insufficiency and stenosis and aortic insufficiency (mild)

Average basal		80	117	65	52	14	6.0	250	192	0.77	36.5	45.6	3.98	4.8	61	
Feb. 16, a.m.	234	104	130	80	40	18	17.7	697	705	1.16	39.6	62.6	9.00	7.8	76	
Feb. 16, p.m.	351	122	140	85	55	27	23.3	1,013	978	0.97	40.3	63.6	9.12	10.9	89	

P. R., a man, aged 42; height, 176 cm.; weight, 69 Kg.; vital capacity, 4,500 cc.; diagnosis, "chronic myocarditis" (?)

Average basal		75	117	85	32	15	6.3	223	189	0.85	38.4	50.0	5.05	3.8	50	
Feb. 15, p.m.	234	117	138	97	41	24	20.4	714	745	1.04	43.5	62.3	7.32	10.2	87	Moderate fatigue
Feb. 19, p.m.	351	135	145	88	57	26	23.9	1,050	957	0.91	43.5	63.5	7.77	12.3	91	Slight fatigue of legs

G. P., a woman, aged 22; height 159 cm.; weight, 55 Kg.; vital capacity, 3,200 cc.; diagnosis, subacute rheumatic fever

Average basal		76	130	70	50	12	5.2	223	174	0.78	37.2	43.6	2.80	6.2	82	
Feb. 11, p.m.	234	126	170	95	75	19	19.7	839	739	0.88	37.5	55.3	7.31	10.1	80	Slight fatigue
Feb. 22, p.m.	351	152	145	70	75	31	27.5	1,053	983	0.93	37.8	57.4	8.03	12.3	81	Moderate dyspnea; no fatigue
Feb. 26, p.m.	351	148	165	80	85	24	24.4	1,030	937	0.91	38.9	59.0	8.27	11.3	77	Moderate dyspnea and palpitation
Feb. 28, a.m.	234	109	140	70	70	23	18.6	808	688	0.85	38.0	55.6	6.89	10.0	99	No fatigue or dyspnea

M. W., a woman, aged 24; height, 153 cm.; weight, 63 Kg.; vital capacity, 3,500; diagnosis, complete heart block

Average basal		43	155	65	90	18	6.1	233	182	0.79	40.3	48.3	3.4	5.4	125	
Feb. 2, p.m.	234	72	180	85	95	31	26.0	877	915	1.04	39.4	58.4	7.72	11.8	164	Marked fatigue and moderate dyspnea
Feb. 19, p.m.	351	87	195	90	105	33	28.7	1,160	1,076	0.93	41.9	63.1	8.28	13.1	149	Marked fatigue and moderate dyspnea

J. A., a man, aged 22; height, 178 cm.; weight, 67 Kg.; vital capacity, 4,200 cc.; diagnosis, complete heart block

Average basal		32	115	55	60	11	4.8	238	184	0.78	39.7	48.8	3.81	4.8	154	
Feb. 13, p.m.	234	37	150	50	100	17	18.0	719	736	1.02	40.9	62.7	8.95	8.2	220	Moderate fatigue of abodminal muscles
Feb. 18, p.m.	351	38	175	68	107	17	21.6	857	995	1.16	43.7	69.2	10.0	9.9	258	Marked fatigue and moderate dyspnea
Feb. 27, p.m.	351	38	165	60	105	16	21.6	1,051	1,000	0.95	42.4	67.7	9.96	10.1	264	Performed experiment easier than above

ten minutes apart gave very constant values for oxygen consumption and carbon dioxide production, minute ventilation, and percentage of oxygen and carbon dioxide in the expired air.

Table 2 gives the average minute ventilation, oxygen consumption, carbon dioxide production and respiratory quotient as obtained from two metabolism periods. The alveolar and venous carbon dioxide tensions are averages of four sets of samples or sometimes three when one is obviously incorrect. The pulse, blood pressure and respiration rates represent averages reached during the steady state. The average of two observations under basal conditions (see paper I) is recorded for the patients with heart disease. Case histories of the patients used in this investigation are given in paper I. The two standard grades of work will be referred to in the results as grade 1 and grade 2 work and will denote 234 kilogram meters and 351 kilogram meters per minute, respectively.

RESULTS

Normal Conditions.—Four normal young men, one of whom was obese, were subjected to the same work that was performed by the patients with heart disease. M. F., aged 29, competed in athletic sports only to the extent of playing tennis during the summer. S. L., aged 38, had not taken any regular exercise in recent years but had competed in some minor sports while in high school. E. H., aged 27, competed in athletic sports and had ridden a bicycle frequently while in high school, but had done very little since that time. The results in these normal persons (see table 1) are not very different from those reported by other observers. After grade 2 work, none of the subjects complained of dyspnea, but M. F. and S. L. complained of some fatigue of the legs. The cardiac output with the heavier work varied in these three persons from 12.6 to 14.8 liters a minute. At the same time, the stroke volume varied between 89 and 121 cc. S. L., who had not had routine exercise for many years, had a higher pulse rate and a lower stroke volume during exercise than the other normal subjects.

R. K., aged 29, a fourth normal subject, differed from the others in that he weighed 215 pounds, or 97.5 Kg. (50 pounds, or 22.7 Kg., overweight), and that he had been very active in track, hockey and football while in college, seven years before these observations were made. Five periods of exercise were performed by this subject. He did not complain of fatigue or dyspnea at any time during exercise, but he did volunteer the information that it required much more effort to perform the first two periods of exercise than the subsequent ones, although the fifth represented a heavier grade of work than the first. The effect of repeated exercise (training) is seen in this patient also in the decreasing rate of respiration, pulmonary ventilation per minute and cardiac output and in the increasing arteriovenous differences. The cardiac output decreased from an average of 14.9 liters per minute with an oxygen consumption of 1,250 cc. a minute in the first experiment to

an output of 12.9 liters a minute with an oxygen consumption of 1,230 cc. a minute in the fifth, notwithstanding the fact that a heavier grade of work was used in the latter. These changes were accompanied by an increase in the arteriovenous difference from 6.11 to 8.08 per cent by volume. Since the arteriovenous carbon dioxide difference is an indication of the coefficient of utilization, an increase in oxygen transport occurred. The respiratory rate decreased gradually from 19 in the first experiment to 6 in the fifth, while the ventilation per minute decreased from 22.4 to 16.9 liters a minute. When the respiratory rate was 6 a minute, the tidal air was 66 per cent of the vital capacity. The low respiratory rates are attributed to the patient's former habit of taking as few breaths as possible when competing in short distance runs. The average respiratory quotient of 0.85 is lower than in any of the other exercising subjects and might be explained on the basis of obesity. It seems unlikely that these changes are merely manifestations of a greater familiarity with the procedures, since they came on gradually after several working periods were performed. The other normal subjects showed somewhat comparable effects after repeated periods of exercise but to a lesser extent, as fewer observations were made. The changes noted in these persons probably represent the effects of training. Bock and his associates [5] have previously pointed out the effects of training in the normal person.

Chronic Rheumatic Valvular Disease.—CASE 1.—*Mitral insufficiency and stenosis.*

F. M., a man, aged 25, had a mild attack of cardiac decompensation with auricular fibrillation in November, 1928, three and one-half months before these studies were begun. Normal rhythm was restored with the use of quinidine sulphate. At the time of these observations, he had no symptoms of cardiac insufficiency; the pulse rate was slow, and there was no enlargement of the heart.

No dyspnea or fatigue occurred when he performed either the light or the heavy grade of work. On grade 2 work, the cardiac output reached 14.8 liters a minute with an oxygen consumption of 1,245 cc. a minute. The stroke volume was 122 cc., and the arteriovenous carbon dioxide difference 7.72 per cent by volume. These results as well as the respiratory reactions were entirely comparable to those of the normal controls. The pulse pressure, however, averaged about 20 mm. of mercury lower than in the control subjects. This was brought about by the small rise in systolic pressure.

CASE 2.—*Mitral insufficiency and stenosis and aortic insufficiency (mild).*

S. T., a youth, aged 16, was known to have had valvular disease for four years previous to these investigations but had never had symptoms of cardiac insufficiency. Examination at the time of these observations showed a normal sized heart with a regular rhythm. The patient was considered to be in good physical training as he played basketball three days a week without unusual fatigue or dyspnea.

He carried out both grades of work with less effort than any other patient, including the normal subjects. On grade 2 work the cardiac output increased to 10.9 liters a minute and 89 cc. a beat, with an oxygen consumption of 1,013 cc. a minute. The arteriovenous carbon dioxide difference of 9.12 per cent by volume

was the highest observed in any case of sino-auricular rhythm. The respiration, minute ventilation and pulse rate were similar to those in the normal controls. The pulse pressure was low, being similar in this respect to that in the preceding patient with mitral stenosis. The type of response seen in this patient probably represents a minimum amount of work to the heart and may be ascribed to the patient's trained condition.

CASE 3.—*Mitral insufficiency and stenosis and aortic insufficiency (advanced).*

I. C., a youth, aged 17, had been in the Peter Bent Brigham Hospital with acute rheumatic fever and pancarditis three and a half years before these studies were made, at which time 400 cc. of fluid was removed from the pericardial cavity. At the time of the present observations he complained of dyspnea on moderate exertion. The pulse was regular, and the heart was markedly enlarged, but there were no signs of congestive failure.

With grade 1 work, he experienced moderate dyspnea and marked general fatigue toward the end of the period. After about fifteen minutes, however, he seemed somewhat recovered, but was forced to remain in bed three days with dyspnea and fatigue. During this time he had several small hemoptyses, and for this reason another period of exercise was not attempted. During work, the cardiac output increased to 11.2 liters a minute with an oxygen consumption of 868 cc. a minute, in spite of the patient's advanced heart disease. The stroke volume of 94 cc. and the arteriovenous carbon dioxide difference of 7.27 per cent by volume were within normal limits. The respirations and the minute ventilation were also normal, although increased figures had been expected because of the dyspnea and fatigue. The pulse rate increased from 78 to 119, and the blood pressure rose from 150 mm. systolic and 40 mm. diastolic to 185 mm. systolic and 60 mm. diastolic. Sounds over the brachial artery could be heard down to a zero pressure, but a change in quality occurred at the diastolic pressures indicated. The general reactions found in this patient were not very different from those in normal subjects but the work was performed with much more effort.

CASE 4.—*Subacute rheumatic fever.*

G. P., a woman, aged 23, when first seen in the fall of 1928, five months before these investigations, complained of palpitation, precordial pain and general fatigue. She had an afternoon fever around 99.6 F. which continued through the winter. The blood pressure fluctuated considerably from time to time. In the spring of 1929, she had an initial attack of acutely inflamed joints typical of rheumatic fever. These studies were carried out two months prior to the onset of the joint symptoms. At this time, examination of the heart showed hyperactive sounds and a slight systolic murmur at the apex.

Four observations were made, the first and last with grade 1 work and the second and third with grade 2 work. Dyspnea and palpitation occurred with the heavier work but were not present with the lighter. The patient never complained of very much general fatigue. The cardiac output increased to an average of 10 liters a minute with an oxygen consumption of about 800 cc. a minute with grade 1 work, while with grade 2 work it averaged 11.8 liters a minute with an oxygen consumption of about 1,000 cc. a minute. The stroke volume did not increase above the basal figure of 82 cc. in the first three observations. This unaltered stroke volume was accompanied by an average pulse rate of 150 during grade 2 work. In observation 4, with a grade of work similar to that in the first period there was an increase in the stroke volume to 99 cc. and a slower pulse rate of 109 a minute. The effect of training is suggested by these more normal reactions and by the greater ease with which the latter work was accomplished. The respiration reached 31 a minute and the minute ventilation 27.5 liters in period 2, but such a rise was not observed during other periods of exercise.

TABLE 3.—*The Response of the Pulse and Blood Pressure to Exercise in Patients with Subacute Rheumatic Fever and Complete Heart Block*

Case 4. Subacute Rheumatic Fever

Feb. 22, 351 kilogram-meters
Oxygen consumption, 1,053 cc. per minute
Cardiac output, 12.3 liters per minute
Stroke volume, 81 cc. per beat

	Pulse Rate	Blood Pressure		Pulse Pressure
		Systolic	Diastolic	
Rest	80	108	68	40
Exercise				
1 min.	132	130	66	62
3	132	140	70	70
5	140	144	70	74
7	146	145	70	75
8	144	145	70	75
10	148	144	68	76
12	...	148	68	80
15	154	145	68	77
18	152	144	68	76
22	152	148	70	78
24	Exercise stopped			
25	137	132	75	57
26	108	115	70	45
28	104	105	74	31
31	104	104	70	34
34	90	100	68	32
35	90	104	78	26
38	90			

Feb. 26, 351 kilogram-meters
Oxygen consumption, 1,030 cc. per minute
Cardiac ouput, 11.3 liters per minute
Stroke volume, 77 cc. per beat

	Pulse Rate	Blood Pressure		Pulse Pressure
		Systolic	Diastolic	
Rest	76	135	88	47
Exercise				
2 min.	136	144	74	70
5	140	168	78	90
7	142	168	80	88
10	142			
14	144	165	80	85
15	148	164	78	86
17	148	164	75	89
22	156	165	70	95
23.5	Exercise stopped			
24	156	162	74	88
26	122	158	80	78
27	110	138	84	54
29	106	136	90	46
33	96	136	88	48
35	104	134	88	46
38	96			

Case 6. Complete Heart Block

Feb. 2, 234 kilogram-meters*
Oxygen consumption, 877 cc. per minute
Cardiac output, 11.8 liters per minute
Stroke volume, 164 cc. per beat

	Pulse Rate	Blood Pressure		Pulse Pressure
		Systolic	Diastolic	
Rest	58	160	75	85
Exercise				
3 min.	68	180	85	95
5	70	180	85	95
7	72	185	85	100
12	78	180	85	95
16	75	185	85	100
21	70	178	78	100
25	72	180	80	100
26	Exercise stopped			
28	60	150	78	72
30	57	148	75	73

Feb. 19, 351 kilogram-meters†
Oxygen consumption, 1,160 cc. per minute
Cardiac output, 13.1 liters per minute
Stroke volume, 149 cc. per beat

	Pulse Rate	Blood Pressure		Pulse Pressure
		Systolic	Diastolic	
Rest	46	144	70	74
Exercise				
1 min.	68	180	80	100
8	82			
10	92	190	90	100
16	88	190	90	100
19	82			
21	..	200	95	105
27	Exercise stopped			
28	60	140	60	80
29	..	140	64	76
33	52	140	70	70
36	52	140	68	72

Case 7. Complete Heart Block

Feb. 13, 234 kilogram-meters
Oxygen consumption, 719 cc. per minute
Cardiac output, 8.2 liters per minute
Stroke volume, 220 cc. per beat

	Pulse Rate	Blood Pressure		Pulse Pressure
		Systolic	Diastolic	
Rest	42	115	58	57
Exercise				
2 min.	38	145	60	85
4	38	145	70	75
6	38	150	60	90
9	36	150	50	100
14	37	144	52	92
17	37	150	50	100
21	..	146	50	96
22	Exercise stopped			
23	41	140	50	90
25	43	130	70	60
26	43	120	70	50
27	..	115	60	55
28	42	120	70	50

Feb. 18, 351 kilogram-meters
Oxygen consumption, 857 cc. per minute
Cardiac output, 9.9 liters per minute
Stroke volume, 258 cc. per beat

	Pulse Rate	Blood Pressure		Pulse Pressure
		Systolic	Diastolic	
Rest	38	120	65	55
Exercise				
2 min.	30	140	68	72
4	36	155	68	87
9	38	180	70	110
12	38	180	68	112
14	38	180	65	115
18 (aur.	126)‡			
21 (aur.	126)	160	65	95
22	40			
24	Exercise stopped			
24.5(aur.	134)	155	60	95
25	42			
27	42	140	70	70
29	40	125	70	55
32	40	120	70	50

Feb. 27, 351 kilogram-meters
Oxygen consumption, 1,051 cc. per minute
Cardiac output, 10.1 liters per minute
Stroke volume, 264 cc. per beat

	Pulse Rate	Blood Pressure		Pulse Pressure
		Systolic	Diastolic	
Rest	36	115	70	45
Exercise				
3 min.	34	145	55	90
5	34	150	52	98
8	36			
9 (aur.	134)	170	60	110
14	38	165	65	100
16	37	170	58	112
18 (aur.	130)			
19	38	165	55	110
22	Exercise stopped			
23	..	140	60	80
27	44	130	70	60
30	40	115	70	45

* About five extrasystoles per minute during exercise.
† Very numerous extrasystoles during exercise.
‡ Auricular rate counted by venous pulsations.

An interesting manifestation of the instability of the vasomotor system is seen in the second and third observations performed four days apart under very similar conditions (table 3). The circulatory response was almost the same except for the blood pressures. In the second observation, the resting blood pressure of 108 mm. systolic and 68 mm. diastolic rose to 148 mm. systolic and 70 mm. diastolic; in the third observation, the resting blood pressure of 135 mm. systolic and 88 mm. diastolic rose to 168 mm. systolic and 80 mm. diastolic. Thus it can be seen that the resting systolic pressure was 27 mm. higher in the latter working period. In both experiments, the blood pressure dropped back almost to its exact resting level after exercise was stopped. In each instance, the pulse rate failed to reach its former resting level after a fifteen minute rest period on the bicycle.

CASE 5.—*"Chronic myocarditis" (?).*

P. R., a man, aged 43, was admitted to the Peter Bent Brigham Hospital in December, 1928, two months previous to these studies, with a history of dyspnea on exertion of several months' duration. Examination revealed auricular fibrillation, a normal sized heart, and a positive blood Wassermann reaction. Normal rhythm was restored by the use of quinidine sulphate. At the time of these observations, two months after discharge from the hospital, there were no symptoms or signs of cardiac insufficiency, and the rhythm was regular.

The muscular work caused some fatigue of the legs but no dyspnea. The cardiac output reached 12.3 liters a minute with an oxygen consumption of 1,050 cc. a minute. The stroke volume, arteriovenous carbon dioxide difference, respiration, minute ventilation and pulse rate reacted as in the normal subjects. The pulse pressure of 57 mm. of mercury during grade 2 work was lower than in the normal subjects and in this respect the patient was similar to the two patients with mitral stenosis (cases 1 and 2).

CASE 6.—*Complete heart block.*

M. W., a woman, aged 24, visited the outpatient department in January, 1929, one month before these studies were begun. The only complaint was backache. There was a history of diphtheria with complete heart block as a complication at the age of 5. Physical examination revealed a pulse rate of 48 and a slightly enlarged heart. An electrocardiogram showed complete auriculoventricular block.

Observations were made, the two standard grades of work being used. Moderate dyspnea and marked fatigue occurred, especially with grade 2 work. With this work, it seemed doubtful whether the patient would be able to finish the period of exercise, and afterward she stated that it was the maximum of which she was capable. No cyanosis or distention of the jugular veins was observed while she was exercising. The cardiac output increased to 13.1 liters a minute with an oxygen consumption of 1,160 cc. a minute on grade 2 work. The stroke volume increased from 125 cc. in the basal state to 149 cc. during the heavier work. With the lighter work, there were fewer extrasystoles than with the heavier, and the stroke volume was 164 cc. During exercise, the arteriovenous carbon dioxide difference did not exceed normal values. The respiratory rate of 33 and the minute ventilation of 28.7 liters were comparable to those in patient 4, who had a rheumatic infection. The heart rate (table 3) with the first grade of work rose from 58 to an average of 72 a minute, and the rise was accompanied by about six extrasystoles a minute. On grade 2 work, the heart rate rose from 46 to an average of 87 beats a minute. This was accompanied by numerous extrasystoles which made the heart seem totally irregular; its rate could be determined only by direct auscultation. An electrocardiogram, taken at another time directly following mild exercise, showed an increase in the ventricular rate from 40 to 50, while the auricle increased its rate from 90 to 120. The auricular and ventricular rhythms were completely

dissociated and no extrasystoles occurred. During grade 2 work on the bicycle, the blood pressure increased from 144 mm. systolic and 70 mm. diastolic to 195 mm. systolic and 90 mm. diastolic, resulting in the high pulse pressure of 105 mm. This case illustrates a type of complete heart block in which the ventricular rate is capable of increasing by the same percentage as that of a normal person. This increase was due both to a regular ventricular acceleration and to ventricular extrasystoles, and served in maintaining an adequate blood flow during muscular activity.

CASE 7.—*Complete heart block.*

J. A., a man, aged 22, was found to have complete heart block in July, 1927, seven weeks after an infection of the foot. A year and a half later, when these studies were made, he was able to be moderately active without symptoms. The heart was slightly enlarged and the rate was 36 a minute. An electrocardiogram showed complete auriculoventricular block.

With the lighter grade of work there was no dyspnea, but he complained of moderate general fatigue and epigastric discomfort. In two observations with the heavier work, the patients experienced moderate dyspnea and quite marked fatigue, the effects of which persisted for several days. No cyanosis was noted during the exercise. The cardiac output was 8.2 liters a minute with an oxygen consumption of 719 cc. a minute on grade 1 work. With the heavier grade of work, it reached 10.1 liters a minute with an oxygen consumption of 1,051 cc. a minute. This was the lowest output observed in any subject in the series on grade 2 work, and was probably due to the inability of the ventricle to increase its rate. The stroke volume reached the very high level of 264 cc., which is a reflection of the failure of the ventricular rate to increase. Liljestrand and Zander [8] stated that the highest stroke volume reported in the literature is 208 cc., which was observed by Lindhard [13] in an athlete when the oxygen consumption was 3,204 cc. a minute. In our case, the arteriovenous carbon dioxide difference reached 10 per cent by volume, the highest figure in this series. This was brought about by a rise in the venous carbon dioxide tension to 69.2 mm. of mercury. The respiratory rate and the minute ventilation were within normal limits. The heart rate, during the resting period on the bicycle, ranged from 36 to 42 a minute (table 3). Immediately after exercise was begun, the heart rate decreased from 2 to 4 beats a minute. After about ten minutes of exercise it returned to its resting level. When exercise was stopped, there was an immediate increase in the heart rate of from 4 to 6 beats, after which it gradually fell back toward its resting level. During work, the jugular veins were distended and auricular pulsations, which were plainly visible, averaged about 130 beats a minute. The blood pressure reaction, typically shown in the third observation, was 115 mm. systolic and 70 mm. diastolic in the preliminary rest period, while during exercise it rose to an average of 165 mm. systolic and 60 mm. diastolic. This patient illustrates the type of heart block in which the ventricular rate does not increase under exertion. An increased cardiac output is maintained by the high stroke volume, and the oxygen supply to the tissue is aided by the increased coefficient of utilization.

COMMENT

It can be seen in table 4 that the cardiac output in all subjects varied between 10.1 and 14.8 liters a minute while they were performing a

13. Lindhard, J.: Ueber das Minutenvolum des Herzens bei Ruhe und bei Muskelarbeit, Arch. f. d. ges. Physiol. **161**:233, 1915.

grade of work of 351 kilogram meters a minute on the stationary bicycle ergometer. There were no very significant differences in the cardiac output between the normal subjects and the patients with heart disease. The lowest values occurred in patient 2, a youth in good physical training with mild valvular disease, and in patient 7, who had complete heart block. Patient 2 performed the work with great ease, while patient 3 experienced considerable distress and fatigue. In both subjects, the increased oxygen consumption was associated with an unusual increase in the arteriovenous carbon dioxide difference, which indicates a greater oxygen exchange between the blood and the tissues. It appears that the trained person (patient 2) performed the work in a very economical fashion. The difficulty that patient 7 experienced in performing the work might be attributed to the changes in cardiac function that accompany the 100 per cent increase in the output of the heart without an increase in the ventricular rate.

TABLE 4.—*Cardiac Output, Pulse Rate, Stroke Volume and Pulse Pressure of Normal Subjects and of Patients with Heart Disease While Performing Work Amounting to 351 Kilogram Meters a Minute* *

Subject		Cardiac Output, Liters per Minute	Heart Rate per Minute	Stroke Volume, Cc.	Pulse Pressure, Mm. Hg.
M. F.	Normal	14.8	122	121	75
S. L.	Normal	13.6	130	105	70
E. H.	Normal	14.4	120	120	77
R. K.	Obese normal	12.9	107	120	60
F. M.	Mitral stenosis	14.8	121	122	56
S. T.	Mitral stenosis; aortic insufficiency	10.9	122	89	55
P. R.	Chronic myocarditis	12.3	135	91	57
G. P.	Subacute rheumatic fever	12.3	152	81	75
M. W.	Heart block	13.1	87	149	105
J. A.	Heart block	10.1	38	264	105

* Patient 3 is omitted, as the grade of work was too strenuous for him.

With an increase in cardiac output such as was seen in these cases, a slow pulse rate was associated with a high stroke volume, and vice versa, as would be expected. This phenomenon is illustrated in its most marked form in patient 7, who had complete heart block, and in patient 4, who had subacute rheumatic fever. Patient 7 could not increase his pulse rate above 38 beats a minute, and since the cardiac output was 10.1 liters a minute, the stroke volume was thereby increased to 264 cc. Patient 4 had a heart rate of 150 a minute during exercise. This resulted in an average stroke volume of 79 cc. (two observations), which was slightly below the resting level. Both patients performed the work with some dyspnea and fatigue. In the normal subjects or in those with more normal responses, the pulse rate and stroke volume both approached a figure of 120 for the heavier grade of work. No general correlation apparently existed between the blood pressure and the stroke volume. In the patients with heart block, however, the pulse pressure showed an appreciable increase along with the high stroke volume.

Peabody and Sturgis [14] found an increased oxygen consumption and pulmonary minute ventilation in patients with heart failure when at rest. No significant difference in the oxygen consumption and minute ventilation was observed between our patients, who had compensated heart disease, and the normal subjects. The two women, however (patients 4 and 6), had higher respiratory minute volumes than the men, with approximately the same oxygen consumptions. We cannot assume that these higher values were related to the cardiac condition, as no observations were made in women with normal hearts.

The respiratory quotients were for the most part between 0.90 and 1. In two instances (patients 7 and 2), we observed average values of 1.16, which were approximately the same at the beginning and at the end of the periods of exercise. In repeated observations, the respiratory quotients for these two patients were 0.95 and 0.97, respectively. The explanation of this discrepancy is not clear.

Vital capacities were taken at rest and again just before exercise was stopped. Little difference was noted in the two records. Patients who experienced some dyspnea during exercise showed the following average variations in the vital capacities from the resting levels: Patient 3, an increase of 100 cc.; patient 4, a decrease of 100 cc., and patient 6, a decrease of 600 cc.; patient 7 showed no change. Except for patient 6, who had complete heart block, the changes in the vital capacity during rest and exercise were negligible. If any change in the pulmonary blood volume occurred in the patients with mitral stenosis, it was not shown by changes in the vital capacities.

Values for the carbon dioxide tension of the arterial and venous bloods during exercise are shown in table 2. A marked rise occurred in the venous carbon dioxide, while the alveolar carbon dioxide showed only a slight increase or remained unchanged. The arteriovenous difference, then, was increased largely by the rise in the venous carbon dioxide. This observation is of interest when compared with changes in the arteriovenous differences of patients studied at rest. It was shown in paper I that changes in the arteriovenous difference in carbon dioxide accompanying variations in the cardiac output at rest are the result principally of changes in the arterial carbon dioxide level.

When the increased arteriovenous difference of carbon dioxide found during exercise is interpreted in terms of oxygen exchange, it means that there is an increase in the coefficient of oxygen utilization. The increased oxygen demand is met, therefore, by an increase both in the

14. Peabody, F. W., and Sturgis, C. C.: Clinical Studies on the Respiration: IX. The Effect of Exercise on the Metabolism, Heart Rate, and Pulmonary Ventilation of Normal Subjects and Patients with Heart Disease. Arch. Int. Med. **29**:277 (March) 1922.

output of the heart and in the coefficient of utilization. We have already suggested that training seems to increase the coefficient of utilization. The circulation, then, may be more economical as a result of training, since it allows the increased oxygen demand during exercise to be met by a greater oxygen utilization, with less blood required by the tissues.

In our studies we have shown that the cardiac output responded to a standard grade of work in a similar manner in normal persons and in those with compensated heart disease. This is consistent with the work of some authors who have found that the output of the heart is a function of the respiratory metabolism. If the heart could not have maintained an adequate circulation with the grade of work used, a cumulating oxygen debt would have ensued and exercise could not have been contined for a long period. Although the response of the cardiac output was quite similar in all of the subjects studied, several of the patients with heart disease experienced dyspnea, fatigue and general distress, symptoms that were almost negligible in the normal subject. These adverse subjective reactions were not related to any considerable variation in the measurable cardiac output.

It is a striking fact that the subjective symptoms accompanying work in patients with cardiac disease are very evident when the several measurable factors of these observations change essentially as they do in those with normal hearts under the same conditions of work. There are yet some unknown factors present in the circulatory mechanism of patients with heart disease. These are manifested by symptoms of dyspnea and fatigue on exertion but are, at the present time, unmeasurable by determinations of the cardiac output, stroke volume, vital capacity or respiratory minute ventilation.

SUMMARY

1. Four normal subjects and seven patients with compensated heart disease, including chronic rheumatic valvular disease, subacute rheumatic fever, "chronic myocarditis" (?) and complete heart block, were subjected to two moderate, standardized grades of work on the Krogh bicycle ergometer. Measurements were made of the cardiac output, pulse rate and blood pressure during exercise.

2. The response of the cardiac output in the patients with heart disease was not essentially different from the response in the normal subjects. The lowest values occurred in a youth in good physical training with mild valvular disease who performed the work with ease, and in a young adult with complete heart block who performed the work with difficulty.

3. Four of the patients with heart disease experienced fatigue and dyspnea during exercise. Fatigue was usually more marked than dyspnea.

The first patient had advanced aortic and mitral disease with marked cardiac enlargement. The pulse pressure, which was abnormally high at rest, increased relatively as in the normal subjects during exercise. The second patient, who had subacute rheumatic fever, had an abnormal increase in the pulse rate, while the stroke volume did not rise above its basal level. In the third, a young woman with complete heart block, the pulse rate doubled during exercise. This was effected both by an increase in the ventricular rate and by the occurrence of extrasystoles. The fourth patient, a young man with complete heart block, had a slight decrease in the pulse rate during exercise. This was accompanied by a greatly increased stroke volume, higher than any previously reported in the literature. Both patients with complete heart block had an unusual rise in the pulse pressure during work.

4. The effect of training is indicated by the more efficient response seen in a patient with mild valvular disease who had been accustomed to strenuous exercise, and in several of the other subjects after they had performed repeated periods of work on the bicycle.

THE SIGNIFICANCE OF AXIS DEVIATION IN THE HUMAN ELECTROCARDIOGRAM

A COMPARISON OF ELECTRICAL AXIS WITH ROENTGEN RAY AND CLINICAL OBSERVATIONS IN THREE HUNDRED AND THIRTY-FOUR CASES *

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For purposes of understanding the significance of electrical axis or axis deviation, the heart may be regarded as a strip of muscle. If the two electrodes of a galvanometer make contact at *A* and *B* of a muscle strip (fig. 1), and the current runs parallel to and in the plane of the electrodes, a deflection occurs. If the electrodes are at *X* and *Y*, the electrical fields at these points approach a balance, little or no difference of potential is present, and practically no deflection occurs. For purposes of simplification, contacts *A-B* may be likened to lead I, and points *X-Y* to lead III. If three leads are so arranged as to form an equilateral triangle, an idea of the position of the muscle strip may be obtained by comparing the height of the deflections in the three leads. In figure *2 A*, it is noted that lead II lies in the direction of the muscle strip, and is therefore in a position to record maximum voltage and greatest deflection. When the muscle strip lies horizontal, as in figure *2 B*, lead I will record the greatest difference of potential; in the position shown in figure *2 C*, the maximal excursion will be indicated in lead III. In a similar manner, by noting the respective heights of the R waves in the human electrocardiogram, one can obtain an idea of the general position of the electrical axis of the heart.

In well defined left axis deviation, the R wave is relatively high in lead I; the S wave, deep in lead III. In right axis deviation, the relation is reversed, the R wave being high in lead III and the S wave deep in lead I. These variants may be employed to portray in a general way the electrical axis of the heart. Two general methods for determining this axis have come into use. One expresses the axis in terms of degrees of an angle; the other, as an index.

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The first method of determining electrical axis was introduced by Einthoven,[1] who expressed this axis as an angle (angle alpha) which is arbitrarily measured from a horizontal plane, as in figure 3 (modified from Einthoven). This angle is determined by a consideration of the height of a certain deflection at a given time simultaneously in the three

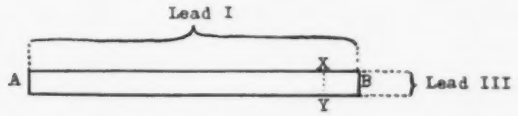

Fig. 1.—Diagrammatic sketch of heart illustrating deflection caused by the contact of two electrodes at *A* and *B*, with the current parallel to, and in the plane of the electrodes. If the electrodes are at *X* and *Y*, little or no deflection occurs.

Fig. 2.—Illustration of the deflection due to the position of the muscle strip. In figure *2 A*, lead II lies in the direction of the muscle strip and records maximum deflection. In figure *2 B*, the muscle strip lies in a horizontal position and lead I records the greatest difference in potential. In figure *2 C*, the maximal excursion is indicated in lead III.

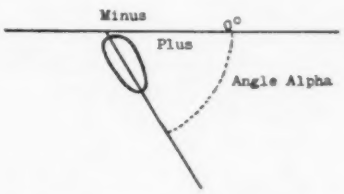

Fig. 3.—Diagrammatic illustration of the first method of determining electrical axis, by expressing this axis as angle alpha.

leads. He has shown mathematically that if one regards the three leads as the sides of an equilateral triangle, the value of any point of the QRS complex in lead II will be equal to the sum of the values of the

1. Einthoven, W.; Fahr, G., and de Waart, A.: Ueber die Richtung und die manifeste Grösse der Potentialschwankungen in Menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch. f. d. ges. Physiol. **150**:275 (March) 1913.

simultaneous points in leads I and III.[2] When the peaks of only two waves are approximately in phase, the value in the third lead may be obtained by the formula: lead II = lead I + lead III. In right predominance, the peaks of the R waves in leads II and III are usually found to be practically in phase, whereas in left predominance the peaks of the R waves in leads I and II generally occur almost simultaneously. The values of the R peaks may then be taken as the values e_1, e_2 and e_3 of Einthoven's formulas and the electrical axis determined as an angle accordingly. Or, the value of the highest peak may be reduced to a scale of 10, the others reduced correspondingly, and, using Einthoven's tables,[3] the degree of the angle determined. Einthoven considered an angle between 40 and 90 degrees as normal, below 40 degrees as constituting left deviation and above 90 degrees as right deviation. Waller[4] has suggested —10 degrees to 100 degrees as normal limits. A modification of Einthoven's method has been presented by Carter,[5] who takes 0 to 90 degrees as normal limits, as does Dieuaide.[6]

The other general method of determining axis deviation is by means of an index, as suggested by Lewis.[7] Lewis' formula is as follows: $(R_1 + S_3) - (S_1 + R_3) = \text{Index}$. R and S are expressed as the heights in tenths of a millivolt of these waves in the respective leads indicated by the numerals. A value above + 20 is considered left axis deviation; below — 15, right deviation. White's formula, $(U_1 + D_3) - (D_1 + U_3)$ is similar, U corresponding to the upward deflection and D to the largest of the downward deflections, whether it be Q, R or S. Pardee[8] has critically compared these methods of Einthoven, Carter, Lewis and White.

There are differences of opinion concerning the value of the electrical axis as an index of relative hypertrophy of the ventricles. Present knowledge is based on the following correlations: (1) a comparison of the axis deviation with the relative weights of the heart chambers

2. Einthoven, W.: Weiteres über das Elektrokardiogram, Arch. f. d. ges. Physiol. **122**:558, 1908.

3. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, New York, Paul B. Hoeber, Inc., 1925, p. 204. Einthoven (footnote 1).

4. Waller, A. D.: Proc. Roy. Soc., London **88**B:49 (Aug.) 1914.

5. Carter, E. P.; Richter, C. P., and Greene, C. H.: A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, Bull. Johns Hopkins Hosp. **30**:162 (June) 1919.

6. Dieuaide, F. R.: The Determination and Significance of the Electrical Axis of the Human Heart, Arch. Int. Med. **27**:558 (May) 1921.

7. Lewis, T.: Observations on Ventricular Hypertrophy with Especial Reference to Preponderance of One or Other Chamber, Heart **5**:367, 1913.

8. Pardee, H. E. B.: Determination of Ventricular Preponderance from the Electrocardiograph, Arch. Int. Med. **25**:638 (June) 1920.

determined post mortem; (2) a comparison of the axis with clinical observations—for example, hypertensive heart disease usually gives rise to relatively greater hypertrophy of the left ventricle, while pulmonic and mitral stenosis generally produce relative hypertrophy of the right ventricle; (3) a comparison of the axis with an orthodiagram of the heart.

The first method is obviously the most exact. Thus far, however, the total number of such correlations has not exceeded 74 (Lewis,[7] Cotton,[9] Herrmann[10]). A comparison with clinical observations should be of value if the number of cases is large, and the clinical diagnoses are well founded. Such a study has been made by Bridgman,[11] White and Bock[12] and White and Burwell.[13] A comparison of electrical axis with orthodiagrams alone is the least satisfactory method for the reason that hypertrophy of one or the other chamber is not necessarily made evident by the teleoroentgenogram.

Soon after Einthoven[14] pointed out the relation of deviation to preponderance, many considered this relation almost constant. This idea was further strengthened by the observations of Lewis,[7] who, by comparing the electrocardiograms with the postmortem weights of each ventricle separately in nine cases, showed that, barring slight deviations, left axis deviation usually meant left-sided preponderance, and that right axis deviation even more constantly meant right-sided hypertrophy or relative preponderance. This work was substantiated by Cotton[9] in a study of six additional cases. White and Bock,[12] using Lewis' formula for axis deviation, compared clinical diagnoses with electrocardiograms in 104 cases. They found that in 26 cases showing marked deviation to the right or left (over + 30 and beyond — 18) all the right deviations occurred in cases of mitral stenosis, rheumatic heart disease with stenosis, congenital heart disease, or chronic emphysemas, whereas all left deviations occurred in either aortic regurgitations or hypertensive hearts without aortic regurgitation. They found also that in 3 of 7 cases with slight right axis deviations the hearts were normal

9. Cotton, T. F.: Observations on Hypertrophy, Heart **6**:217, 1915.

10. Herrmann, G. R., and Wilson, F. N.: Ventricular Hypertrophy: A Comparison of Electrocardiographic and Postmortem Observation, Heart **9**:91, 1922.

11. Bridgman, E. W.: The Value of the Electrocardiogram in the Diagnosis of Cardiac Hypertrophy, Arch. Int. Med. **15**:487 (March) 1915.

12. White, P. D., and Bock, A. V.: Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, Am. J. M. Sc. **156**:17 (July) 1918.

13. White, P. D., and Burwell, C. S.: The Effects of Mitral Stenosis, Pulmonic Stenosis, Aortic Regurgitation and Hypertension on the Electrocardiograph, Arch. Int. Med. **34**:529 (Oct.) 1924.

14. Einthoven, W.: Le télécardiogramme, Arch. internat. de physiol. **4**:132, 1906.

while in only 8 of 61 cases of slight left axis deviations was this true. White and Burwell [13] reviewed 288 cases of right axis deviation and 398 of left axis deviation and obtained similar results. The observations of White and Bock, and White and Burwell then appeared to attach a real clinical significance to axis deviation, and their work indicated that cases of marked deviation bear a fairly constant relation to definite clinical conditions. They compared only the clinical observations with the electrocardiogram and did not consider the size and position of the heart. Carter and Greene [15] concluded from clinical impressions and from the work of Lewis and Cotton that the electrocardiogram is the only satisfactory method of estimating relative preponderance, and that, considered with the teleoroentgenogram, it is a valuable guide to gross hypertrophy. Pardee [8] suggested a relationship between axis deviation and the position of the heart in the chest and believed this relationship would account for certain apparent discrepancies between axis deviation and ventricular preponderance.

The work of Herrmann and Wilson,[10] however, has thrown doubt on the clinical interpretation of axis deviation. Using a technic similar to Lewis' for determining the weights of the ventricles, and studying a larger series of fifty-nine cases, they concluded that relative weight is only one of many factors influencing electrical axis, and that it predominates only when the heart is greatly hypertrophied. They thought the disturbing factors to be (*a*) variations in the position of the heart, (*b*) variations in arrangements of conducting systems and (*c*) disturbances of atrioventricular conduction. They accounted for the discrepancy between their conclusions and those of Lewis by the fact that all the hearts in Lewis' series were large, and in very large hearts the relative weight is the chief factor influencing axis deviation.

Fahr [16] has maintained that the form of the electrocardiogram in enlargement of one side or the other is due to increased length of the conducting path in one or the other ventricle. If this is true, dilatation must also be considered in the production of axis deviation. Cohn and Raisbeck,[17] also Meek and Wilson,[18] showed experimentally that changes in position may produce appreciable changes in axis. Meek and Wilson emphasized the significance of rotation of the heart on its

15. Carter, E. P., and Greene, C. H.: The Electrocardiogram and Ventricular Preponderance, Arch. Int. Med. **24**:638 (Dec.) 1919.

16. Fahr, G.: Analysis of Spread of Excitation Wave, Arch. Int. Med. **25**: 146 (Feb.) 1920.

17. Cohn, A. E., and Raisbeck, M. J.: Relation of Position of Enlarged Heart to Electrocardiograph, Heart **9**:331 (Dec.) 1922.

18. Meek, W. J., and Wilson, A.: The Effect of Changes in Position of the Heart on the Q R S Complex of the Electrocardiogram, Arch. Int. Med. **36**: 614 (Nov.) 1925.

longitudinal axis in influencing this deviation. Reid [19] has recently concluded from a comparison of 100 orthodiagrams with electrocardiograms that the axis is no satisfactory guide to relative ventricular hypertrophy.

It would appear, then, from an analysis of the literature that the problem of the value of axis deviation is still unsettled. In the present study, the electrical axis is compared with both the roentgenologic observations and clinical diagnoses in 334 cases. The electrical axis was determined by finding the angle alpha according to Einthoven [1] (fig. 3). The two largest R waves were generally chosen, but only when their peaks appeared approximately at the same moment in the cardiac cycle. The patients were for the most part ambulatory. The majority of the roentgenograms taken were orthodiagrams and the remainder were plates of the heart taken at a distance of 2 meters. They were taken with the patient in the erect position; the electrocardiograms, in the recumbent position. The cardiac measurements and electrocardiograms were in almost all cases taken within the same week. The records used showed no evidence of disturbance in conduction. The patients regarded as having hypertension showed a minimal systolic pressure of 170 mm. of mercury.

In the following analysis, the degree of deviation is designated normal when it is between 40 and 90 degrees; slight left when 20 to 40 degrees; moderate left, 0 to 20 degrees; marked left, below 0 degree, and right, above 90 degrees. The enlargements of the heart are classified as left, generalized or right. A further classification is made of left enlargements as slight, moderate and marked. Enlargements were all definite; the questionable variations were rejected. Otten's [20] orthodiagraphic standards were used.

NORMAL HEARTS

Of the 68 hearts which were normal roentgenographically and clinically, 46 (or 67 per cent) had normal angles; 14 (or 21 per cent) showed slight left deviation; 6 (or 9 per cent) moderate left deviation, and 2 (or 3 per cent) marked left deviation. Thus it is seen that only 12 per cent of the normal hearts had angles below 20 degrees and only 3 per cent below 0 degree. It is interesting to note that no normal heart in this series showed an angle over 80 degrees.

The positions of the heart were classified as vertical, oblique or transverse. Although it is fairly certain that change in position is a

19. Reid, W. D.: Comparison of Electrical Axis Shown by Electrocardiograph with Roentgen Mensuration, Am. Heart J. **4**:223 (Dec.) 1928.

20. Otten, M.: Die Bedeutung der Orthodiographie für die Erkennung des beginnenden Herzweiterung, Deutsches Arch. f. klin. Med. **105**:370, 1911.

factor in determining electrical axis, nevertheless varying positions as ordinarily observed in the roentgenogram were found not to be paralleled with any degree of regularity by changes in axis. For example, several normal hearts with definitely vertical positions showed angles below 70 degrees. Also, no constant relationship was noted between the electrical axis and the transverse position of the heart.

PATHOLOGIC HEARTS OF NORMAL SIZE

Twenty-seven hearts of normal size were classed as definitely pathologic on clinical examination. Twelve of these were cases of hypertensive heart disease, three showing normal angles, three slight left deviations and six moderate left deviations. Eleven were cases of arteriosclerotic heart disease. One of these had a normal angle, 2 showed slight left deviation, 4 moderate left deviation, and 3 marked left deviation. There

TABLE 1.—*Enlarged Hearts*

	Marked Left	Moderate Left	Slight Left	Normal	Slight Right 80-90	Right
Rheumatic mitral stenosis	2	2	3	14	7	9
Hypertensive heart disease	23	32	21	7	..	..
Syphilitic aortic regurgitation	2	..	..	1	..	..
Congenital pulmonic stenosis	..	..	..	1	..	5
Chronic emphysema	..	..	..	..	..	1
Others	10	17	16	33	1	..
Totals	37	51	40	56	8	15

were 4 cases of mitral stenosis, and all showed normal angles. The angle in one of the latter was 88 degrees. Thus, only 8 of 27 pathologic hearts of normal size presented normal angles.

ENLARGED HEARTS

There were 207 definitely enlarged hearts with the following clinical diagnoses: essential hypertension, 83; rheumatic heart disease, 37; syphilitic aortic regurgitation, 3; congenital heart disease, 6; chronic emphysema, 1, and miscellaneous, 77 (table 1). Of the 83 patients with hypertension, 76 showed left deviation varying from slight to marked, while only 7 had normal angles. This type of heart disease is, of course, commonly associated with left ventricular preponderance. According to Lewis'[7] postmortem studies, relative left ventricular preponderance is found more constantly in hypertensive heart disease than in any other type. Of the 3 syphilitic hearts with aortic regurgitation, 2 showed marked left deviation and 1 a normal axis. There were 37 enlarged hearts with rheumatic mitral stenosis. Of these, 21 were normal, 7 ranging between 80 and 90 degrees. In 9 the angle was above 90 and in 7 below 40 degrees. Of the latter, 4 were associated with aortic insufficiency and 1 with hypertension. Of 6 with congenital heart

disease, 5 showed right axis deviation, and in 1 the angle was normal. All enlarged hearts with right axis deviation presented either mitral stenosis, congenital heart disease or chronic emphysema.

COMPARISON OF ROENTGENOGRAM WITH ELECTRICAL AXIS

In this series, there appear no significant relationships between the orthodiagraphic heart size and electrical axis. For example, of 87 enlarged hearts, the gross roentgen ray appearance of which was much the same, namely, left-sided enlargement, there were 37 with marked left axis deviation and 50 with normal angles. Of the 21 cases of right-sided predominance from the roentgen ray standpoint, 1 showed slight left deviation and 13 normal angles, while only 7 gave definite electrocardiographic signs of right preponderance. Of 103 hearts of normal size, 47 were within the normal limits and 56 showed slight to marked left deviation.

TABLE 2.—*Distribution of Axis According to Size of Heart*

Size	Below 0	0-10	10-20	20-30	30-40	40-80	80-90	Over 90
Normal	7	8	12	6	23	45	2	..
Questionable enlargement	4	1	4	4	3	7	..	..
Slight enlargement	19	9	15	12	10	27	2	2
Moderate enlargement	9	13	7	4	6	14	..	3
Marked enlargement	9	3	4	4	3	9	..	3
Principally right enlargement	..	..	..	..	1	7	6	7

These observations do not indicate that axis deviation is without significance, since the orthodiagram is not a satisfactory indicator of relative ventricular preponderance. As Bardeen [21] has indicated, only hypertrophy as a whole can be determined by roentgen ray examination. It follows, then, that a comparison of roentgen ray observations alone with electrical axis is of little or no value, and that conclusions based on this correlation are not justified.

PROPOSED CHANGE OF NORMAL LIMITS

In the present series there were 68 normal hearts. Not one of these showed an angle as high as 80 degrees. Of the 10 cases with angles between 80 and 90 degrees, 8 were cases of mitral stenosis and 6 of these appeared definitely enlarged to the right on the orthodiagram. This indicates that 80 degrees might be considered the upper limit of right deviation, rather than 90 degrees as suggested originally by Einthoven. This is in accordance with the views of White and Burwell,[18] who, after observing for many years the significance of axes determined by Lewis' formula, felt that — 10 instead of — 15 degrees

21. Bardeen, C. R.: Determination of the Size of the Heart by Means of X-Rays, Am. J. Anat. **23**:423 (March) 1918.

should be the borderline of normal with respect to right axis deviation. Such a change in the Lewis formula corresponds to a change in the angle, as suggested herewith. Further, the fact that a number of normal hearts show angles between 0 and 40 degrees warrants the acceptance of zero degree as the limit of left deviation rather than 40 degrees as proposed by Einthoven. The foregoing observations therefore suggest that 0 to 80 degrees be regarded as the limits of normal axis deviation, with the possibility in infrequent cases of limits of —10 and 90 degrees.

SUMMARY AND CONCLUSIONS

1. The present status of the clinical significance of axis deviation in the human electrocardiogram is reviewed. The electrical axes, orthodiagrams and clinical observations are compared in 334 cases.

2. Clinical conditions generally associated with left ventricular preponderance tend to produce left axis deviation; those associated with right ventricular preponderance more constantly produce right deviation. This occurs more regularly in enlarged hearts than in hearts of normal size.

3. Sixty-six of 68 normal hearts on clinical and orthodiagraphic examination presented angles varying from 0 to 80 degrees. Zero to 80 degrees is therefore proposed as the limits of normal with the possibility in infrequent cases of limits of — 10 to 90 degrees.

I. THE DIFFUSIBLE CALCIUM AND THE PROTEINS OF THE BLOOD SERUM IN JAUNDICE*

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Investigations into the state of the blood calcium in diseases accompanied by jaundice have been carried out mainly in three directions: the direct examination of the total calcium content of the whole blood, serum or plasma of jaundiced patients and experimental animals; the determination of the toxicity of bile and bile salts as modified by the action of calcium salts, and the injection of these into the blood stream of experimental animals; and by therapy with calcium salts, cod liver oil and ultraviolet radiation, and by the action of extract of parathyroid hormone in experimental animals and in man.

The most consistently and most widely quoted works are those of King and Stewart,[1] Lee and Vincent,[2] Vines,[3] Groves and Vines,[4] Kirk and King[5] and Walters and Bowler.[6] It is largely on the basis of these investigations, in which the three methods of approach mentioned were employed, that the current opinion rests for the existence of a deficiency in available calcium of the blood of jaundiced patients.

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* This research is one of a series carried out jointly by the Department of Medicine and the Division of Biochemistry of the University of California Medical School, with the cooperation of Professors W. J. Kerr and Carl L. A. Schmidt.

1. King, J. H., and Stewart, H. A.: Effect of the Injection of Bile on the Circulation, J. Exper. Med. **11**:673, 1909.

2. Lee, R. I., and Vincent, B.: The Relation of Calcium to the Delayed Coagulation of the Blood in Jaundice, Arch. Int. Med. **16**:59 (July) 1915.

3. Vines, H. W. C.: The Coagulation of the Blood; I. The Rôle of Calcium, J. Physiol. **55**:86, 1921.

4. Grove, W. R., and Vines, H. W. C.: Calcium Deficiencies, Their Treatment by Parathyroid Extract, Brit. M. J. **1**:791 (May 20) 1922.

5. Kirk, P. L., and King, C. G.: Calcium Distribution in the Blood, J. Lab. & Clin. Med. **11**:928 (July) 1926.

6. Walters, W., and Bowler, J. P.: Preoperative Preparation of Patients with Obstructive Jaundice, Surg. Gynec. Obst. **39**:200 (Aug.) 1924.

The examinations of the total calcium content of the whole blood, plasma and serum have, in the hands of different workers, yielded variable results in the investigations on jaundice. The workers on the modifying action of calcium salts on the toxicity of bile are not in accord. The proponents of the existence of a deficiency in the available calcium of the blood in jaundice quote with considerable emphasis the work of Kirk and King. With the exception of these authors, this group base their proof for the existence of a calcium deficiency on indirect evidence, such as the purported decrease in the clotting time of the blood of jaundiced patients obtained after therapy with agents that are known to increase the diffusible calcium content of the blood. Since there is a lack of accord, and some of the work goes back as far as 1909, ten years or more before a satisfactory method was developed for the estimation of small amounts of calcium in biologic fluids, it is well at this time to evaluate the reports of such observations.

TABLE 1.—*Results from King and Stewart* [1] *Purporting to Show Absorption of Calcium by the Bile Pigments Circulating in the Blood Stream*

	Normal Blood*	Blood of Jaundice*	Remarks
I	0.050 Gm. calcium	0.060 Gm. calcium	20 per cent increase
II	0.045 Gm. calcium	0.053 Gm. calcium	16 per cent increase
		0.060 Gm. calcium	20 per cent increase

* These results are probably expressed as grams of calcium per liter of blood, which would be equivalent to 5 and 4.5 mg. per hundred cubic centimeters, values that are compatible with the established lower values for whole blood.

CRITICAL REVIEW OF THE LITERATURE

In 1909, on the basis of an analysis of the blood calcium in two dogs, King and Stewart [1] concluded that the bile pigments circulating in the blood in obstructive jaundice gradually absorb the calcium of the organs and tissues to form calcium compounds which diminish the amount of available calcium in the tissues. They determined one normal value for the calcium content of the blood in each of two dogs and then tied off the common bile duct. In one case, a single analysis of blood was made after the experimental jaundice was produced, and in the second, two determinations of calcium were made after the jaundice was produced. Since their methods of analysis were not described and they did not show how their results were expressed, it is difficult to survey critically their experimental data (table 1), unless it is assumed that they expressed their values in grams of calcium per liter of blood. This apparently is what they did, for if one assumes that they ashed whole blood of dogs, their normal value could be read as 5 and 4.5 mg. per cent, respectively, and these results would be compatible with the lower values for whole blood of dogs. Conclusions were based on a 20 per cent change in experimental values,

apparently without a consideration of the normal limits of variations in such analyses. It is now well known that whole blood, depending on the volume occupied by the red blood corpuscles [7] or the hematocrit, as it is now expressed, may vary in man from 5.3 to 6.8 mg. per cent,[8] by difference, a variation of 28 per cent over the lower value. The range for serum calcium in dogs is close to that found in human beings. The 20 per cent change found by King and Stewart may still be within the normal range of variation and otherwise not be of significance. As the methods for the analysis of small amounts of calcium in biologic fluids were far from satisfactory at that time and up until the publications of Kramer and Howland [9] in 1920, and of Kramer and Tisdall in 1921 [10] and 1922,[7] the work of King and Stewart remains valuable mainly because of its historical interest. But even as late as 1927, quotations from this work were to be found as argument to justify conclusions that significant alterations in the blood calcium exist in jaundiced patients.[11]

Observations on the state of the blood calcium in jaundice have been confusing, and the difficulty of interpretation has been increased by the use of the words "ionic" and "ionizable" in describing analytic methods for the determination of the total calcium [12] content of the whole

7. Kramer, B., and Tisdall, F. F.: Distribution of Sodium, Potassium, Calcium and Magnesium Between Corpuscles and Serum of Human Blood, J. Biol. Chem. **53**:241, 1922. Rothwell, C. S.: Calcium Determination in Whole Oxalated Blood, J. Biol. Chem. **74**:257 (Aug.) 1927. Stewart, C. P., and Percival, G. H.: Calcium in Corpuscles, Plasma and Serum, Biochem. J. **22**:548, 1928.

8. Kramer, B., and Tisdall, F. F.: The Direct Quantitative Determination of Sodium, Potassium, Calcium and Magnesium in Small Amounts of Blood, J. Biol. Chem. **48**:223 (Sept.) 1921.

9. Kramer, B., and Howland, J.: Method for Determination of Calcium in Small Quantities of Blood Serum, J. Biol. Chem. **43**:35 (Aug.) 1920.

10. Kramer, B., and Tisdall, F. F.: A Clinical Method for the Quantitative Determination of Calcium and Magnesium in Small Amounts of Serum and Plasma, Bull. Johns Hopkins Hosp. **32**:44 (Feb.) 1921.

11. Cantarow, A.; Dodek, S., and Gordon, B.: Calcium in Jaundice with Special Reference to the Effect of Parathyroid Extract on Distribution of Calcium, J. Coll. Phys. **49**:132, 1927; Calcium Studies in Jaundice, with Special Reference to Effect of Parathyroid Extract on Distribution of Calcium, Arch. Int. Med. **40**:129 (Aug.) 1927.

12. The term total calcium is used here to denote the value found on analysis of serum or whole blood, which has stood from 6 to 24 hours, after the addition of a soluble oxalate salt, such as is used in the methods based on the Kramer and Tisdall method for the analysis of serum calcium. For a discussion of the reaction that occurs when calcium is precipitated in serum by the addition of oxalates, consult Stewart and Percival (footnote 8).

blood, the serum or the plasma by procedures such as that described by Vines [3] and that recently by Tweedy and Koch.[13] If calcium exists in the plasma or serum, partly in the ionic form as Ca^{++} ion, and partly in the nonionized form in combination with protein,[14] as there is good reason to believe it does,[15] if sufficient time elapses after the addition of oxalates, the following equation goes completely to the right to form a precipitate of calcium oxalate and unbound protein (relative to calcium).

$$(1) \qquad Ca^{++} + Ca\ Protein \longleftrightarrow 2Ca^{++} + Protein.$$

$$(2) \quad Ca^{++} + C_2O_4^{--} + Protein \rightarrow CaC_2O_4\ precipitate + Protein.$$

The result is a precipitation of the total amount of the calcium in the serum, plasma or blood, including the ionic, nonionic and protein-bound. Of this amount, only part is ionic or ionized.[16] The clinician may not always discriminate with ease the refinement in terminology and the difference between calcium bound to protein that is potentially ionizable from calcium that is actually in the ionic form. Those methods which depend on the precipitation of calcium in the serum or blood by the direct addition of oxalates, determine not only the small ionic fraction, but the protein-bound potentially ionizable calcium as well, or the total calcium. Such methods yield values that lie in the average range of from 9 to 11 mg. per hundred cubic centimeters for human beings,[17] with extreme values of from 8.5 to 11.7 mg. per hundred cubic centimeters.[18] The methods of Vines [3] and of Tweedy and Koch [13] furnish values that fall within these ranges. On this, we refer the reader also to Stewart and Percival,[7] who discussed and criticized the work of Vines and also presented a discussion of the factors which are involved in the precipitation of calcium from serum by the addition of an oxalate solution.

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13. Tweedy, W. R., and Koch, F. C.: A Suggested Modification of the Kramer and Tisdall Method for the Microchemical Estimation of Ionizable Calcium in the Blood Plasma, J. Lab. & Clin. Med. **14**:747 (May) 1929.

14. Loeb, R. F., and Nichols, E. G.: Effects of Dialysis and Ether Extraction on Diffusibility of Calcium in Human Blood Serum, J. Biol. Chem. **74**:645 (Sept.) 1927. Greenberg, D. M.: The Electrical Transference of Calcium in Blood Serum Protein Solutions, J. Biol. Chem. **79**:177 (Sept.) 1928.

15. Stewart, C. P., and Percival, G. H.: Calcium Metabolism, Physiol. Rev. **8**:283 (July) 1928.

16. Neuhausen, B. S., and Pincus, J. B.: A Study of the Condition of Several Inorganic Constituents of Serum by Means of Ultrafiltration, J. Biol. Chem. **57**: 99 (Aug.) 1923.

17. Myers, V. C.: Practical Chemical Analysis of Blood, ed. 2, St. Louis, C. V. Mosby Company, 1924, p. 170.

18. Criep, L. H., and McElroy, W. S.: Atopy, Arch. Int. Med. **42**:865 (Dec.) 1928.

The recent work of Cantarow and his associates [11] purported to show that a deficiency of calcium existed in the whole blood of jaundiced patients. Their analyses of whole blood were done by a method of their own,[19] in which they attempted to determine the total calcium of whole blood by the direct oxalate precipitation of laked blood, without first removing the cellular débris or the proteins. Their values given as from 6.5 to 9.5 mg. per hundred cubic centimeters are high when compared with the accepted values of from 5.3 to 6.8 mg. obtained by Kramer and Tisdall.[8] The latter figures for whole blood have been confirmed both by Rothwell [20] and by Stewart and Percival.[7] Rothwell pointed out the necessity of removing the cellular detritus of whole laked blood before the calcium could be determined in the presence of protein. By the method of Caven and Cantarow,[19] a small precipitate of cellular detritus was thrown down with the calcium oxalate precipitate. This caused their results to be higher than any reported by the other accepted methods for whole blood, but they felt that their error was a constant one and that their results were comparable within their own standard for normal values.

In analyses of whole blood for calcium done according to their method and of plasma and serum done by a standard procedure, after the injection of parathyroid hormone, they obtained, on the same patient, a parallel change in the whole blood and plasma calcium values without a similar type of change in the serum calcium value. Since it has been amply demonstrated that the plasma and serum calcium values are identical when the ordinary concentration of anticoagulants is used to obtain the plasma, and that the red blood cells contain insignificant amounts of calcium,[7] it is difficult to harmonize such divergent observations. As Cantarow and his co-workers themselves called attention to the fact that their method for whole blood utilized a standard for the normal that was valuable only when the results of the method were compared with its own standard, a comparison of values utilizing widely different standards for the normal values offers itself as a possible explanation for their divergent results. Yet these authors drew their conclusions that the wide variations in the whole blood calcium as opposed to the relative fixation of the serum calcium must be dependent largely on the varied amounts of functionally available and diffusible fractions of the calcium and on the bile pigments that bind the calcium fraction and are excreted in the urine.

In consideration of the factors enumerated, the conclusions reached by Cantarow and his associates, that a deficiency exists in the available

19. Caven, W. R., and Cantarow, A.: A Method for the Determination of Calcium in Whole Blood, J. Lab. & Clin. Med. **12**:76 (Oct.) 1926.

20. Rothwell, C. S. (footnote 7, second reference).

and diffusible calcium of the blood in patients with jaundice, cannot be accepted as proved.

Analysis of Diffusible Calcium in Jaundice.—The improvements [21] in the method of Moritz [22] for the determination of the diffusible calcium of the blood serum has placed in our hands a more exact method for the determination of the state of the available calcium than can be offered by analysis of the total calcium of the serum, plasma or whole blood. It has been indicated by Neuhausen and Pincus [16] and Stewart and Percival [7] that the water-clear, protein-free ultrafiltrate contains the same concentration of ionic calcium as the blood serum, but all the ultrafiltrate is not ionized. Various workers have shown that the analysis for diffusible calcium of the blood serum, which normally varies between extremes of 4.2 and 6.8 mg. per hundred cubic centimeters of the ultrafiltrate, is a better measure of the physiologically available calcium than the analysis for total calcium.[23]

The utilization of the analysis for ultrafiltrable calcium in the study of the state of the calcium in jaundice has to our knowledge been attempted only by Kirk and King.[5] On the basis of four analyses in the case of apparently normal persons, they found that the diffusible calcium constituted from 70 to 75 per cent of the total calcium of the serum with an average value of 72.3 per cent. This range is much higher than that given by other authors,[24] whose figures usually show between 45 and 55 per cent of the serum calcium to be diffusible. In jaundice, they found that only 55 per cent of the calcium was diffusible as against the 72 per cent which they considered as normal. A critical examination of their data, table 2, reveals changes that are apparent rather than actual. They are apparent because the values of ultrafiltrable calcium were expressed in terms of percentage of the total calcium. If the values of the ultrafiltrable calcium are recalculated to be expressed similarly in terms of concentration, it will be seen that their data do not show alterations in the concentration of the diffusible calcium significant enough to be outside the region of normal variation. Their

21. Greenberg, D. M., and Gunther, L.: On the Determination of Diffusible and Nondiffusible Serum Calcium, J. Biol. Chem. **85**:491 (Jan.) 1930.

22. Moritz, A. R.: The Effect of Ultraviolet Radiation on the State of the Serum Calcium, J. Biol. Chem. **54**:81, 1925.

23. Stewart and Percival (footnote 15); Moritz (footnote 22); Liu, S. H.: A Comparative Study of the Effects of Various Treatments on the Calcium and Phosphorus Metabolism in Tetany; Chronic Juvenile Tetany, J. Clin. Investigation **5**:259 (Feb.) 1928.

24. Greenberg and Gunther (footnote 21); Liu (footnote 23, fourth reference); Updegraff, H.; Greenberg, D. M., and Clark, G. W.: A Study of the Distribution of the Diffusible and Nondiffusible Calcium in Blood Sera of Normal Animals, J. Biol. Chem. **71**:87 (Dec.) 1926.

low values for the total calcium in jaundice are in agreement with our results. We will show later that such values are due to a fall in the nondiffusible fraction of the calcium which may be explained by a decrease in the serum proteins.

Updegraff, Greenberg and Clark [24] pointed out that the usual procedure of reporting the value of the diffusible calcium in terms of percentage of the total serum calcium may be misleading; for the diffusible calcium has, in a normal person under a given condition, a practically fixed value, whereas the concentration of the nondiffusible calcium fluctuates within comparatively wide limits. The value of the diffusible

TABLE 2.—*Results by Which Kirk and King* [5] *Purported to Show a Low Diffusible Calcium in Jaundice* *

Total Calcium Mg. per 100 Cc. Serum	Percentage, Ultrafilterable Calcium / Total Calcium	Calculated Diffusible Calcium, Mg. per 100 Cc.	Remarks
8.49	67.4	5.7	Normal
7.58	67.7	5.2	Normal
9.24	80.9	7.5†	Normal
7.43	72.3	5.3	Normal
9.80	45.95	4.5	Jaundice
11.39	55.1	6.3 (serum)	Jaundice
7.85	66.5	5.2	Jaundice
4.31 (?)	50.6	2.2 (serum)‡	Jaundice
6.94	59.9	4.1 (serum)	Jaundice
7.91	64.0	5.0	Jaundice
8.52	48.2	4.1 (serum)	Jaundice
7.49	58.5	4.4	Jaundice

* They attempted to obtain the diffusible calcium of whole blood by the use of an organic anticoagulant, but in certain instances clotting occurred, and the diffusion was continued on serum without altering the final results. The values reported as percentage of the total serum calcium as shown by the ultrafilterable calcium, indicated apparent changes in jaundice. The same data recalculated, as in the third column, with one exception, showed the concentration of the diffusible calcium to be within the limits reported for the normal. The data also show two irregular results compatible with inconstant collodion membrane preparations.

† A very high value for the normal. Most likely the error here was the leakage of serum through the collodion membrane.

‡ This value is extremely low, and was probably due to an impermeable membrane. No mention was made of tetany.

calcium expressed in terms of percentage of the total serum calcium will therefore fluctuate and create an impression that it is undergoing a change when this may not be the case. On the other hand, the value of the diffusible calcium when expressed in terms of concentration of calcium in the ultrafiltrate will not show these apparent changes. Liu,[25] in his studies on chronic juvenile tetany, demonstrated the clinical importance of expressing the value of the diffusible calcium in terms of concentration rather than as a percentage of the total calcium. The diffusible calcium in tetany varied within a narrow range between 3.1 and 3.4 mg. per hundred cubic centimeters, while the total calcium of the serum of the same specimens varied between 6.5 and 9 mg. per hundred cubic centimeters, as the result of variations in the nondiffusible fraction. The average value in tetany could be expressed as 50 and 36 per cent.

respectively, of the total serum calcium and thus show wide changes that were not actually present. The stability of the concentration of diffusible calcium for a given condition has also been shown in our own studies on parathyroid tetany, in which a similar fixation of the diffusible calcium at a low level was found accompanying large variations in the total calcium due to fluctuations in the nondiffusible calcium fraction.

If one recalculates the data of Kirk and King [5] (table 2) to express their results in terms of concentration of calcium in the ultrafiltrate rather than in terms of percentage of the total serum calcium, it can be seen that in seven of eight jaundiced patients (including two with values of 4.1 mg.) the concentration of the diffusible calcium falls within the normal range of 4.2 and 6.8 mg. per hundred cubic centimeters. One value is obviously incorrect, being so low that it would be compatible only with the existence of tetany. It may be safely stated from the values reported for juvenile tetany by Liu [23] and from our studies on parathyroid tetany that values for the diffusible calcium below 3.4 mg. per hundred cubic centimeters (unless one is dealing with poor collodion membrane preparations) are accompanied either by acute or chronic symptoms of tetany. Kirk and King made no mention of such symptoms, and it may be safely assumed that such symptoms were not present.

A further perusal of table 2 reveals wide deviations in certain of their analyses, which probably indicates inconstant action in the collodion membranes used. We have pointed out [21] that variable results, either values too high owing to serum leaking through the membrane (their value of 7.5 mg. per hundred cubic centimeters for one of their normal persons may be due to this cause) or values too low owing to failure of the membrane to permit diffusion (their low results of 3.4 and 2.5 mg. per hundred cubic centimeters in the absence of symptoms of tetany, are of this type), will be obtained if the collodion mixture is not proper. We have suggested a formula for collodion, or a collodion preparation that allows a constant ultrafiltration to be obtained.[21]

A critical review of the results of Kirk and King [5] shows that the concentration of the diffusible calcium in the serums of six of eight patients with jaundice is within the normal range of variation. The results of the investigations by Kirk and King into the state of the diffusible calcium in jaundice fail to show significant alterations from the normal values for the concentration of the ultrafiltrable calcium of the blood of jaundiced patients.

The Detoxification of Bile Pigments by Calcium Salts.—A second method of approach by which it has been deduced that a deficiency of calcium exists in the blood of jaundiced patients has been through observations on the delayed coagulation of blood in vitro after the addition of bile; [1] or through observations on the antagonistic action of

calcium salts on the delay in coagulation occasioned by the addition of bile,[2] and by the observations on the coagulation of blood after the injection of bile pigment into the circulation, with or without a preliminary treatment with calcium salts to effect a detoxification of the bile.[1]

The experimental results in the detoxification of bile and bile salts by the action of soluble calcium salts are not in agreement. Meltzer and Salant [25] as early as 1905 pointed out that confusion of results was obtained in the in vivo injection of bile, depending on the rate of injection and the concentration of the bile entering the blood stream. Even Lee and Vincent,[2] who supported the view that in the in vitro experiments soluble calcium salts in weak concentrations have an antagonistic action on the delayed clotting time occasioned by the addition of bile to blood, pointed out that bile also affected other elements involved in coagulation. Recently, Emerson [26] reinvestigated the results of the experiments with in vivo injection and found that soluble calcium salts had no appreciable detoxifying effect on bile, and concluded that the beneficial effects of the administration of calcium chloride in obstructive jaundice as a preoperative preparation are due to effects other than its action as a detoxifying agent.

Shortening of Coagulation Time by Therapy Aimed at Increasing the Blood Calcium.—A deficiency of calcium in the blood of jaundiced patients has also been claimed because of the effect of calcifying agents on the coagulation time. This method of approach to the problem has been through observations of the action of soluble calcium salts in jaundiced patients in whom there was present a delay in coagulation time. It has been claimed that such therapy shortens the clotting time in jaundiced patients [27] and reduces the operative mortality [6] when used as a preoperative measure in patients with obstructive jaundice. Calcium chloride and parathyroid extract have also been found to be of value in controlling hemorrhages from various causes.[28]

Conclusions based on such evidence must necessarily be indirectly arrived at because there is little, if any, experimental proof of the actual existence of a deficiency of available calcium. Such conclusions are furthermore open to objection because it has been claimed that

25. Meltzer, S. J., and Salant, W.: Studies on the Toxicity of Bile, J. Exper. Med. **7**:280, 1905.

26. Emerson, W. C.: The Effect of Calcium Chloride on the Toxicity of Bile, J. Lab. & Clin. Med. **14**:714 (May) 1929.

27. Walters, W.: Preoperative Preparation of Patients with Obstructive Jaundice, Surg. Gynec. Obst. **33**:651 (Dec.) 1921.

28. Vines (footnote 3); Walters (footnote 27); Gordon, B., and Cantarow, A. J.: Use of Parathyroid Extract in Hemorrhage, J. A. M. A. **88**:1301 (April 23) 1927.

soluble calcium salts injected into the blood stream may temporarily shorten the coagulation time even in normal persons.[29] Zimmerman[30] recently reinvestigated the effect of an increase in the total blood calcium obtained through the injection of parathyroid hormone in jaundiced and nonjaundiced dogs and human beings. He did not find a decrease in the clotting time in either condition concomitant with the increase in the blood calcium and concluded that calcium salts per se do not shorten the coagulation time in jaundice. Similar results were obtained by one of us in jaundiced and nonjaundiced patients, by the use of Walters and Bowler's[6] regimen of calcium chloride administration as a preoperative measure.[31] The contention that the administration of calcium salts as a preoperative measure shortens the coagulation time cannot be accepted as proved. If this is true, its corollary, that there is a deficiency of calcium in jaundice, likewise must be viewed with suspicion. Recent workers are tending toward this view, as shown by the remarks of Ravdin,[32] who also could find no evidence of alterations in the calcium fractions of the blood serum in human beings and in dogs with jaundice.[33] He and Morrison also studied the coagulation time in jaundiced patients by the Lee and White method and came to the conclusion that the reduction in coagulation time frequently observed during the preoperative preparation of the patient and the fewer postoperative hemorrhages were due to the dextrose used previous to the operation rather than to the calcium salts. They demonstrated, in their own experiments, a marked reduction in the coagulation time of the blood of the jaundiced and nonjaundiced patients and dogs after the intravenous administration of a solution of dextrose. That the intravenous injection of calcium salts causes a similar phenomenon has never been definitely shown in the literature.

Brougher[34] used the therapeutic method of approach to determine the state of the diffusible calcium of the blood in jaundice. He did not analyze the blood of his animals for the concentration of the ultrafiltrable calcium, but argued from a decrease in clotting time following

29. Coleman, C. J.: The Coagulation of Blood and the Effect of Certain Drugs and Toxins upon It, Biochem. J. **2**:184, 1907.

30. Zimmerman, L. M.: Effect of Parathyroid Hormone on Blood Coagulability. With Special Reference to Jaundice, Am. J. M. Sc. **174**:379 (Sept.) 1927.

31. Unpublished work done at the Kaspare Cohn Hospital, Los Angeles, with the assistance of Dr. J. R. Lacoe.

32. Ravdin, I. S.: Some Aspects of Carbohydrate Metabolism in Hepatic Diseases, J. A. M. A. **93**:1193 (Oct. 19) 1929.

33. No data were given regarding the results of their analyses for calcium.

34. Brougher, J. C.: The Effect of Cod Liver Oil on the Delayed Coagulation Time Following Experimental Obstructive Jaundice, Science **68**:256, 1928.

the administration of cod liver oil to jaundiced dogs that the diffusible calcium was at fault. Liu,[35] he pointed out, showed that cod liver oil increased both the fractions of the serum calcium, the diffusible and the nondiffusible, the former being increased more than the latter. From this fact Brougher argued that it was rational to use cod liver oil to hasten coagulation of the blood "in jaundiced animals in which diffusible or available calcium is low"; thus he stated as a fact an assumption which had yet to yield to experimental proof, for till then no actual work had been done outside of the observations of Kirk and King,[5] discussed heretofore, on the analysis for the ultrafiltrable calcium of the blood in jaundice.

Brougher concluded that the efficacy of cod liver oil in causing the shortening of the clotting time in jaundice that he observed was probably based on its ability to increase the ionizable calcium. Since there is at present no satisfactory method for the determination of ionized calcium, one can do little else but conjecture as to the variations of ionic calcium under cod liver oil therapy. But the condition of the diffusible calcium in jaundice is susceptible of experimental proof, and pure conjecture based on indirect observation is not permissible. The results of our experiments and observations on the state of the diffusible calcium in jaundice will now be stated.

EXPERIMENTAL PROCEDURE

Our studies were made on eleven adults who were jaundiced from various causes. In every case in which it was practicable, studies were made on the total and diffusible calcium of the serum, the inorganic phosphate of the serum, the serum albumin and globulin, the serum icteric index and the bleeding time (Duke) and the clotting time of the blood. Generally, 20 cc. of blood was collected for analysis from the cubital vein of the arm, in the morning after a fast of one night. Moderate stasis was employed by means of a tourniquet. A large needle, gage 19, was used to ensure rapid collection of the specimen. The serum was removed within from four to twelve hours after the specimen was collected. We have found[21] that no change in the total and diffusible calcium can be detected even after twenty-four hours, if the serum is allowed to stand in contact with the clot in a tightly stoppered tube.

The general procedure was to use, in the following order, 2 cc. of serum for the determination of total calcium, 0.5 cc. for that of the serum proteins, 4 or 5 cc. for ultrafiltration, and 2 cc. for the determination of inorganic phosphate. The inorganic phosphate determination was not set up until we were satisfied that 4 or 5 cc. of serum was available for filling the collodion membrane[36] for ultra-

35. Liu, S. H.: The Partition of Serum Calcium into Diffusible and Non-Diffusible Portions, Chinese J. Physiol. **1**:331 (July) 1927.

36. The preparation of the collodion membrane is of the utmost importance. We have reported elsewhere (footnote 21) the method for the preparation of satisfactory membranes.

filtration. If the amount of serum that remained was insufficient to allow 2 cc. for the determination of inorganic phosphate, this analysis was performed on the supernatant fluid obtained from the first centrifugation of the total calcium precipitate, according to the method described by ourselves.[37] (If the total amount of serum available does not amount to more than 3 or 4 cc. the system of analysis discussed elsewhere by the authors [footnote 21] can be used to give results satisfactory for clinical usage.) The icteric index, bleeding time and clotting time were found independently within a short time of the drawing of the specimen for analysis.

Methods.—The analyses for total calcium were done on the serum by Tisdall's modification[38] of the Kramer and Tisdall method.[39] The ultrafiltrate was analyzed for diffusible calcium by the same method, modified, however, by the authors[21] to prevent the loss of crystals that might float on the protein-free fluid after the centrifugation. The final analyses were done, in most instances, according to the gasometric method of Van Slyke and Sendroy.[40] A few samples of total and diffusible calcium were titrated with five thousandths-normal potassium permanganate, freshly diluted from a tenth-normal or a hundredth-normal solution. We have checked the titration against the gasometric procedure and when employing samples with calcium equivalent to that in 2 cc. of normal blood serum, have obtained agreement within the error of the titration method, and often to 1 or 2 per cent. The serum was analyzed for proteins by the colorimetric method of Greenberg.[41] The bleeding time was found according to the method of Duke,[42] and the clotting time by the method of Lee and White.[43] The icteric index was determined by the usual procedure. All analyses for phosphate were based on the Fiske and Subbarow method.[44]

The experimental data are shown in table 3. Although we have expressed the concentration of the diffusible calcium as per hundred cubic centimeters of serum, we have found that it does not matter whether the nondiffusible fraction is obtained by separate analysis of the concentrate that remains in the bag after ultrafiltration is completed, or by the subtraction of the value for the calcium of the ultrafiltrate from the value for the total serum calcium. Within the limits of error of our methods of analysis, the concentration of calcium in the ultrafiltrate is the concentration of the diffusible calcium of the serum, for the calcium in the

37. Gunther, L., and Greenberg, D. M.: A Note on the Determination of the Inorganic Phosphate of the Serum on the Filtrate from Calcium Analysis, J. Biol. Chem. **82**:551 (May) 1929.

38. Tisdall, F. F.: A Note on the Kramer-Tisdall Method for Determination of Calcium in Small Amounts of Serum, J. Biol. Chem. **56**:439 (June) 1923.

39. Kramer, B., and Tisdall, F.: A Simple Technique for the Determination of Calcium and Magnesium in Small Amounts of Serum, J. Biol. Chem. **47**:475 (Aug.) 1921.

40. Van Slyke, D. D., and Sendroy, J., Jr.: Gasometric Determination of Blood Calcium, Proc. Soc. Exper. Biol. & Med. **24**:167 (Nov.) 1926.

41. Greenberg, D. M.: The Colorimetric Determination of the Serum Proteins, J. Biol. Chem. **83**:545 (May) 1929.

42. Todd, T. C.: Clinical Diagnosis by Laboratory Methods, ed. 5 revised, Philadelphia, W. B. Saunders Company, 1924, p. 251.

43. Lee and White, in Todd, T. C.: Clinical Diagnosis by Laboratory Methods, ed. 5 revised, Philadelphia, W. B. Saunders Company, 1924, p. 248.

44. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375 (Dec.) 1925.

TABLE 3.—*Jaundice Studies*

Patient	Calcium*			Inorganic Phosphate*	Albumin*	Globulin*	Bleeding Time, Minutes†	Clotting Time, Minutes‡	Icteric Index	Duration of Jaundice	Remarks§
	Total	Diffusible	Nondiffusible								
Group with abnormal bleeding and clotting time											
Rey.	9.3	5.5	3.8	...	...	...	...	11.0	100	18 days	Catarrhal jaundice; Kahn test on the blood, 1 plus
Cant.	8.0	4.9	3.1	3.2	3.4	2.9	...	13.5	100	.....	Toxic jaundice, bronchopneumonia, hyperplasia of thyroid (exophthalmic goiter)
Bles.	8.1	4.5	3.6	4.5	...	...	5.0	....	17.5 25	14 days	Primary carcinoma of cecum, secondary in the liver; fragility of red blood cells from 0.4 to 0.25%
Fras.	7.8	5.1	2.7	2.9	3.6	2.6	2.5	15.0	50	3 months intermittent	Carcinoma of ampulla of Vater; nosebleeds;10 cc. of 5% calcium chloride was administered intravenously daily for three days before the samples of blood were taken; the nosebleeds continued; jaundice was complete for one week before this specimen was taken
Bobe.	10.0 10.0	... 5.3	... 4.7	...	...	...	9.5 9.0	8.0 7.0	133	7 months intermittent	Carcinoma of bile duct; second bleeding and clotting time fourteen days after adequate cholecystgastrostomy
Group with normal bleeding or clotting time.											
Colv.	7.0	4.7	2.4	3.3	3.8	1.7	...	6.5	25	7 days	Toxic jaundice; B. welchii infection of skin following enterostomy for intestinal obstruction
Swe.	8.6	4.5	3.1	3.5	3.5	2.3	2.5	3.5	200	21 days	Carcinoma of head of the pancreas
Trau.	9.4	5.5	3.9	4.5	4.6	1.3	4.75	3.0#	33.5	.....	Congenital familial hemolytic jaundice; fragility of red blood cells; maximum, 0.65%; minimum, 0.45%
Dorn.	10.5	5.4	5.1	...	...	...	3.5	5.8#	200	Not recorded	Portal cirrhosis of the liver ?
Mars.	9.2	6.4	2.8	...	...	...	...	....	60	2-3 days	Carcinoma of the head of the pancreas
Wrigh.	10.3	5.0	...	...	...	...	1.5	4.0#	17	.....	Postoperative convalescence from obstructive jaundice; patient had barely noticeable conjunctival icterus

* All values in milligrams per hundred cubic centimeters of serum.
† By the method of Duke (in Todd, footnote 42).
‡ By the method of Lee and White.[43]
§ All cases from the records of the University of California Hospitals, San Francisco, Calif.
# By capillary tube.

concentrate remaining after ultrafiltration is completed, plus the calcium that diffuses through the membrane equals the concentration of the total calcium of the serum, as may be expressed in the following equation.[21]

$$T_{ca} = \left[\frac{a - x}{a}\right] C_{ca} + \left[\frac{x}{a}\right] F_{ca}$$

Tca, Cca and *Fca* are the symbols for total calcium, concentrate calcium, and ultrafiltrate calcium in milligrams per hundred cubic centimeters or other appropriate units; *a* is the cubic centimeters of serum introduced into the collodion sac, and *x* is the amount of fluid obtained in the ultrafiltration.

RESULTS

The Diffusible Calcium.—The lowest concentration of diffusible calcium found in the blood of jaundiced patients was 4.5 mg. per hundred cubic centimeters and the highest value was 6.4 mg. per hundred cubic centimeters with an average value of 5.16 mg. A study of forty-two analyses on twenty-four medical students and staff members, all apparently in good health, showed variations between 4.2 and 6.8 mg. per hundred cubic centimeters with an average of 4.96 mg. The average for eleven jaundiced patients was 5.16 mg. per hundred cubic centimeters against 4.96 mg. per hundred cubic centimeters for the group of forty-two analyses on apparently healthy medical students, which may serve as the normal measuring rod. Chart 1 shows in a striking manner how the values for the jaundiced patients fall within the zone of the variations found in the normal group.

It appears from this data that a demonstrable deficiency of calcium does not exist in the blood of jaundiced patients as determined by measuring the diffusible calcium of the serum.

The Nondiffusible Calcium.—In jaundiced patients, the nondiffusible calcium of the blood varied from 2.4 to 5.1 mg. per hundred cubic centimeters with an average of 3.68 mg. The nondiffusible calcium in forty-two analyses on medical students and staff members varied between 4.1 and 7.2 mg. per hundred cubic centimeters with an average of 5.07 mg. The zone of variation of the nondiffusible calcium of the blood of jaundiced patients lies well below the zone of variation found for the nondiffusible calcium of apparently normal persons, with an average of 3.68 mg. per hundred cubic centimeters for the jaundiced patients as against an average of 5.07 mg. per hundred cubic centimeters for the medical students. The difference is again shown strikingly in chart 2. These observations, of course, indicate that the average total calcium value of the blood of the jaundiced patients is low, since the sum of the diffusible and the nondiffusible calcium equals the total calcium content of the serum. But this cannot be interpreted as proof for the existence of a deficiency in the available calcium of the serum.

Recent work in the field of diffusible calcium by Stewart and Percival [45] and by Liu [46] indicates that the diffusible calcium rather than the total calcium is a better index of the physiologically active or available calcium. Our data do not show a deficiency in the diffusible calcium in jaundiced patients. The discrepancy between the apparent deficiency

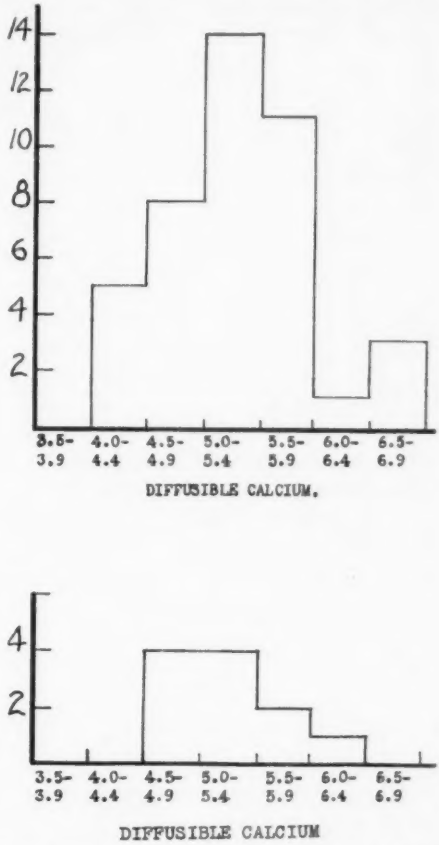

Chart 1.—The variation of the concentration of the diffusible calcium in blood serum in forty-two analyses on apparently normal medical students and staff members, University of California Medical School, upper; in jaundice, lower. Values in milligrams of calcium per hundred cubic centimeters of serum.

of calcium in the blood of jaundiced patients as seen by the values for total calcium, and the abundance of physiologically available calcium as

45. Stewart and Percival (footnotes 8 and 15).

46. Liu (footnote 23, fourth reference, and footnote 35).

demonstrated by the values for diffusible calcium serves to emphasize again, as pointed out by Updegraff, Greenberg and Clark [24] and Liu,[46] that the values for the diffusible calcium of the serum are independent of the values for the total calcium, and serve as a better index of the state of the calcium of the serum. The fluctuations which make the difference in percentage of total calcium shown by the diffusible calcium

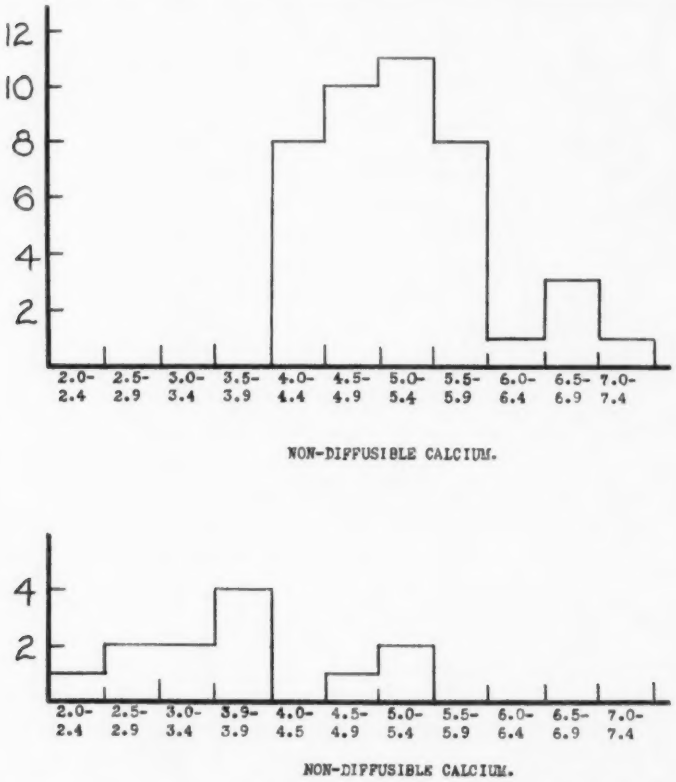

Chart 2.—The variation of the nondiffusible calcium in blood serum in apparently normal medical students and staff members, University of California Medical School, upper; jaundice, lower. Value in milligrams of calcium per hundred cubic centimeters of serum.

in a given person occur in the nondiffusible calcium, which may fluctuate normally over a wide range, while the level of diffusible calcium remains little changed.

The importance of the concentration of the diffusible calcium is nicely demonstrated in diseases known to be due to a deficiency in cal-

cium metabolism. Such diseases as infantile tetany and tetany caused by a deficiency of parathyroid hormone show a diffusible calcium that drops to 3 mg. per hundred cubic centimeters or lower, while the total calcium (due to fluctuations in the nondiffusible calcium) may vary at the same time between 6 and 9 mg. per hundred cubic centimeters. The increase in the nondiffusible calcium, however, shows no effect in the amelioration of the clinical symptoms as long as the diffusible calcium remains low. Now, if there were a deficiency of available calcium in jaundice, one would look for a decrease in the ultrafiltrable calcium such as one finds in diseases that are known to be accompanied by a deficiency in serum calcium. But such a condition was not found in our series of jaundiced patients. The concentration of the diffusible calcium varied between the same limits as observed in forty-two analyses on apparently normal medical students. The nondiffusible calcium, however, was low, and the low values observed were accompanied by a decrease in the values for the serum albumin in the same patient.

The Serum Proteins.—The low nondiffusible calcium observed in our patients with jaundice can qualitatively, at least, be explained by the low serum albumin (table 3). We have observed an analogous fall in the nondiffusible calcium in nephrosis and in other nonhemorrhagic conditions in which there was a marked reduction in the serum proteins. The serum albumin in the jaundiced patients varied between 3.4 and 4.6 mg. per hundred cubic centimeters, with an average of 3.75 mg. Twelve analyses on medical students showed variations between 4.2 and 5.8 mg. per hundred cubic centimeters, with an average of 4.93 mg. per hundred cubic centimeters, and thirteen analyses on adults in whom there was no reason to suspect a deficiency in the serum proteins revealed variations between 4 and 5.9 mg. per hundred cubic centimeters, with an average of 4.85 mg. Rowe,[47] who employed the microrefractometric method of Robertson, found the albumin to vary between 4.6 and 6.7 mg. per hundred cubic centimeters. These observations indicate that the serum albumin in our jaundiced patients was definitely low. If one takes this in conjunction with the obtained average value of 3.68 mg. per hundred cubic centimeters for nondiffusible calcium in the cases of jaundice and 5.07 mg. per hundred cubic centimeters for normal adults, there seems to be a clear connection between the low values of serum albumin and the low values of nondiffusible calcium in these patients. The connection seems valid in spite of the rather few analyses for serum proteins in jaundice presented in our data.

47. Rowe, A. H.: The Albumin and Globulin Content of Human Blood Serum in Health, Syphilis, Pneumonia and Certain Other Infections with the Bearing of Globulin on the Wassermann Reaction, Arch. Int. Med. **18**:455 (Oct.) 1916; cited by Myers, V. C.: Practical Chemical Analysis of Blood, ed. 2, St. Louis, C. V. Mosby Company, 1924, p. 161.

The serum globulin was unchanged in the jaundiced patients. The values varied between 1.3 and 2.9 mg. per hundred cubic centimeters with an average of 2.16 mg. Eleven analyses on medical students and on thirteen apparently normal adults varied respectively between 1.3 and 2 and 1.4 and 2.5 mg. per hundred cubic centimeters, with averages of 2.05 and 2.25 mg., respectively. Rowe's figures were from 1.2 to 2.3 mg. per hundred cubic centimeters, and are comparable with our figures.

The finding of low serum albumin (and low total protein) in all of the jaundiced patients, who also showed low nondiffusable calcium, and therefore low total calcium, is particularly significant, for it has a direct bearing on the present theories on which are based the assumptions that in the blood of patients with jaundice the available calcium is decreased to form nonavailable calcium, or an increase in the protein-bound or bile-protein-bound calcium.

Theories of the Rôle of the Calcium, Protein and Pigment in Jaundice.—King and Stewart,[1] on finding what they thought was an increase in the blood calcium in jaundice, assumed, as an explanation, that the blood calcium united with the bile pigments to detoxify them and was thereby removed as available calcium in its rôle of maintaining the normal bleeding and clotting phenomena. Other workers, Walters and Bowler,[6] Cantarow and his associates,[11] accepting this hypothesis, put forth somewhat modified but similar views and implied, in addition, that the blood calcium then decreased owing to the removal of calcium by the bile pigments.

Kirk and King[5] modified the conception of King and Stewart[1] by tentatively accepting the hypothesis that some of the calcium was bound to the blood proteins, and in jaundice disturbances in the protein balance might affect the degree of diffusibility of the serum calcium. According to this assumption, the diffusible calcium should decrease and the nondiffusible calcium, in turn, increase by becoming bound to protein. Walters and Bowler[6] compromised on these views by stating that the pigment becomes fixed to the plasma proteins to some extent, lessening the diffusibility of the pigment molecule and preventing its excretion. The protein pigment combination uniting with calcium then increases the ratio of protein-bound to free calcium, altering the normal diffusibility and ionic relations. According to this assumption, when the degree of icterus becomes high, the pigment protein combination uniting with the diffusible calcium should decrease this form of the serum calcium, and proportionately increase the nondiffusible form.

We found in our analyses that the bile pigments do not diffuse through the collodion membrane, but remain behind with the proteins. This fact alone places in our hands a particularly effective method of

approach to the determination of the validity of the hypotheses which would bind calcium with bile pigments as jaundice increases, to form nonavailable calcium, or the hypothesis which would bind protein with the diffusible calcium as jaundice increases, or would bind the bile protein combinations with diffusible calcium, each to increase the nondiffusible calcium as jaundice increases. A simple analysis of the concentrate for the proteins and the nondiffusible calcium remaining behind after ultrafiltration would either directly support or refute these assertions. Thus, aside from the actual analysis for the concentration of the diffusible calcium of the blood serum in jaundice, the theories on which are based the assumptions of a deficiency in available calcium lend themselves directly to experimental proof.

In the case "Trau," an analysis of the concentrate in the bag revealed a nondiffusible calcium of 3.72. mg. per hundred cubic centimeters. The nondiffusible calcium obtained by difference was 3.85 mg. per hundred cubic centimeters. These values check within the experimental error of the method.[48] "Trau's" nondiffusible calcium accompanied an icterus which gave a value of 33.5 by the icteric index, and showed a concentration of 3.72. mg. per hundred cubic centimenters, whereas "Swe" with a concentration of pigment which gave an icteric index of 200 showed only 3.05 mg. of nondiffusible calcium per hundred cubic centimeters. These direct experimental observations certainly do not support the hypothesis that an increase in bile pigment decreases the diffusibility of calcium, or binds it in such a fashion as to increase its nondiffusibility. An analysis of the concentrate for its serum proteins gave, in a similar fashion, values identical with the values found in the unconcentrated serum, and no increase in serum proteins was found as the degree of jaundice increased. On the contrary, the serum proteins became low (although there was no direct relation to the severity of the jaundice) owing to a decrease in serum albumin, or were normal. These observation do not confirm the hypothesis that the increasing degree of jaundice binds additional proteins, for the increase in pigment did not increase the serum proteins. The aforementioned results also fail to confirm the assumption that the bile protein combination reduces the diffusibility of calcium by increasing the nondiffusible portion. The nondiffusible fraction by actual analysis and by difference was either normal or low, depending, qualitatively at least, on the serum albumin content.

48. Similar analyses on other patients have shown that the values for the nondiffusible calcium could be arrived at either by subtraction of the values for the diffusible calcium from the values for the total calcium or by an actual analysis of the concentrate. The values obtained by either method agreed within the experimental accuracy of our analytic procedures.

SUMMARY

A critical review of the literature does not reveal sufficient evidence on which to base the conclusion that there exists in the blood of jaundiced patients a deficiency of available calcium, nor is there direct experimental or analytic proof of the existence of a deficiency in the diffusible calcium of the serum.

We have found that the diffusible calcium in the blood of jaundiced patients varies between 4.5 and 6.4 mg. per hundred cubic centimeters. The average value for diffusible calcium in the blood of our jaundiced patients was 5.16 mg. per hundred cubic centimeters as against 4.96 mg. per hundred cubic centimeters determined by forty-two analyses on medical students and staff members who were in good health.

The nondiffusible calcium of the blood of our jaundiced patients varied between 2.4 and 5.1 mg. per hundred cubic centimeters, with an average of 3.68 mg., as compared with variations of 4.1 and 7.2 mg. per hundred cubic centimeters, with an average of 5.07 mg. in apparently healthy medical students. The fall of the nondiffusible calcium was accompanied by a drop in the serum albumin, and can be accounted for, qualitatively, at least, by the decrease in the total serum proteins. The fall in the nondiffusible calcium in certain of the patients cannot be interpreted as a deficiency of available calcium, since ample work in other laboratories, as well as in our own indicates that it is the diffusible fraction of the serum calcium rather than the nondiffusible fraction that is the best measure of physiologically available calcium.

The concentration of the diffusible calcium of the serum remained within the average limits of variation regardless of the degree of jaundice. The nondiffusible calcium was low in four of five patients with a low serum albumin and did not fluctuate in proportion to the degree of jaundice. The total serum proteins did not increase with increasing degrees of jaundice. Our analytic data do not support the hypotheses set forth; namely, the hypothesis of King and Stewart [1] that calcium salts unite with bile pigments to detoxify them and are thereby removed as available calcium; the hypothesis of Kirk and King [5] that in jaundice a disturbance occurs in the protein balance which decreases the degree of diffusibility of calcium; and the hypothesis of Walters and Bowler [6] that the bile pigment becomes fixed to the plasma proteins and the protein pigment combination then unites with calcium to increase the ratio of protein-bound to free calcium, thus altering the normal diffusibility of calcium.

CONCLUSIONS

1. The indirect method of calcium replacement therapy in jaundice should be discarded as a means of proof that the diffusible calcium is

low in jaundiced patients, since a direct analytic method is available for the measurement of the diffusible calcium.

2. Analytic studies of the blood of jaundiced patients show that there is no deficiency in the diffusible calcium of the blood serum, regardless of the degree of jaundice between icteric indexes of 17.5 to 200, and regardless of the absence or presence of abnormal bleeding phenomena.

3. The serum albumin may be low in jaundice.

4. The nondiffusible fraction of the serum calcium may be low as a result of the fall in the serum albumin.

5. The value of the diffusible calcium of the blood serum is a more accurate measure of the physiologically available calcium than the value of either the nondiffusible or the total calcium.

6. Factors other than the amount of available calcium, as measured by the concentration of the diffusible calcium, must be sought to explain the abnormal bleeding phenomena seen in jaundiced patients.

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THE METABOLISM OF OBESITY

VI. THE INFLUENCE OF FATIGUE ON MECHANICAL EFFICIENCY*

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In one of our previous communications,[1] it has been demonstrated that there is a decrease in mechanical efficiency with an increase of obesity. The question arose whether the obese who were accustomed to carry their extra weight had more endurance than the thin or normal subjects and further what effect fatigue would have on their already lowered mechanical efficiency. Clinicians have noted that fatigue seems to be produced more easily in the thin or stout than in those of normal weight. It would seem that a certain amount of adipose tissue is distinctly helpful in the prevention of easy fatigability. Aside from a preliminary report[1] made by us, a perusal of the literature revealed that no similar investigation had been reported. In the present communication, the results of an investigation on the influence of fatigue on mechanical efficiency and the endurance of the three groups are reported.

EXPERIMENTAL WORK

A total of forty-eight experiments were conducted on thirteen obese, fourteen normal and eleven underweight women ranging from 16 to 30 years of age. The weight of the obese subjects in this series varies from 112.7 to 72.3 Kg. (247 to 160 pounds) and averaged 88.9 Kg. (196 pounds). The deviation from the standards[2] was from 110.1 to 19.5 with an average of 55.5 per cent above the normal. The normal subjects weighed from 72.6 to 53.2 Kg. (160 to 117 pounds) and averaged 58.5 Kg. (129 pounds), while the underweight subjects weighed from 50.5 to 38 Kg. (112 to 84 pounds) and averaged 46 Kg.

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1. Wang, Chi Che; Strouse, Solomon, and Morton, Zelma Owen: Studies on the Metabolism of Obesity: V. Mechanical Efficiency, Arch. Int. Med. **45**:727 (May) 1930.

2. Association of Life Insurance Medical Directors and Actuarial Society of America, Medico Actuarial Mortality Investigation, 1912.
published.

(102 pounds). The percentage variations from the standards for the normal group were from + 10.2 to — 8.6 with an average of + 3.2 per cent; those for the undernourished group ranged from — 11.9 to 27.4 with an average of — 18.2 per cent. Mechanical efficiency was determined in the same manner as was described in a previous paper.[1] The first test which measured the heat production while the subject was sitting on the bicycle ergometer, was used as the base line; another test was then made with the person running the ergometer at a speed of about 120 revolutions and with a load of approximately 6 pounds (2.7 Kg.). With the gasometer disconnected, she continued to run the bicycle at the same speed and with the same load until she began to feel tired. At this point, without stopping, she was again connected with the gasometer, and a third test was made. We regret that we did not have a better method for measuring the degree of fatigue than merely the subjects' judgment.

In accordance with our previous observations,[1] tables 1, 2 and 3 show that the mechanical efficiency before fatigue was the lowest in the obese group and the highest in the underweight subjects. With the exception of six of forty-eight experiments, or 12.5 per cent, the mechanical efficiency was lower after the onset of fatigue than before. Thus the percentage averages of the three groups were 19.1, 21.3 and 23.1 as compared with 20.8, 23.7 and 25.7 before the onset of fatigue in the obese, normal and underweight groups. The difference between the mechanical efficiency before and after the onset of fatigue was less marked in the obese group and more pronounced in the other groups. The average differences were 1.7, 2.4 and 2.6 for the three groups, respectively, or 8, 11.8 and 12.6 per cent. The greatest difference of 10.9, or 55.1 per cent, was shown by M. W. in the normal group.

With a decrease of mechanical efficiency after the onset of fatigue, there was also a decrease in the work done per hour. Thus the average values for the three groups before fatigue were 45.4, 54.9 and 45.2 calories per hour for the obese, normal and underweight subjects, respectively. The corresponding values after the onset of fatigue were 43, 49.2 and 43.8 calories.

The endurance of work in the three groups varied greatly, but the general trend seemed to be the lowest in the obese group and highest in the normal group. E. B. and C. G., two of the obese subjects, showed the least endurance of 3.5 minutes, while R. F. of the normal group gave the greatest endurance of 75 minutes. Not only did members of the same group differ widely in their endurance, but the same subjects varied to some extent on different days. Thus A. L. of the obese group gave an endurance of 6, 4.5, 4 and 4 minutes on four different days several months apart. This is also true of C. G. and E. B. of the obese group and M. E. of the underweight group.

TABLE 1.—*Difference in Mechanical Efficiency Before and After the Onset of Fatigue in Obese Subjects*

Subject	Age, Years	Height, Cm.	Weight: Kilograms	Weight: Percentage Deviation from Normal	Heat Production per Hour in Calories: Sitting on Ergometer	Exercising with Brake: Before Fatigue	Exercising with Brake: After Fatigue	Energy Spent on Work: Before Fatigue	Energy Spent on Work: After Fatigue	Work Done per Hour Calories: Before Fatigue	Work Done per Hour Calories: After Fatigue	Work Done per Hour Calories: Difference, per Cent	Mechanical Efficiency: Before Fatigue	Mechanical Efficiency: After Fatigue	Mechanical Efficiency: Difference, per Cent	Endurance, Minutes
A. L.	26	152.1	112.7	+110.1	119	386	355	267	236	46.7	42.0	+11.2	17.5	17.8	— 1.7	4.0
A. L.	26	151.5	104.8	+ 97.0	92	362	345	270	253	40.3	40.8	— 1.2	14.9	16.1	— 7.5	4.0
A. L.	26	151.4	101.0	+ 88.4	97	342	370	245	273	38.5	42.0	— 8.3	15.7	15.4	+ 1.9	4.5
A. L.	26	151.4	98.9	+ 84.4	93	351	357	258	264	46.9	47.0	— 0.2	18.2	17.8	+ 2.2	6.0
E. B.	16	156.9	91.7	+ 73.9	105	349	338	244	233	43.7	41.3	+ 5.8	18.0	17.7	+ 1.7	4.5
M. C.	21	161.9	98.4	+ 73.2	78	313	302	235	224	48.2	41.6	+15.8	20.5	18.6	+10.2	15.0
C. G.	27	164.5	101.8	+ 69.7	77	259	299	182	222	43.1	40.8	+ 5.6	23.7	18.4	+28.8	12.0
E. B.	16	157.2	89.1	+ 67.5	109	308	328	199	219	46.4	45.6	+ 1.8	23.3	20.8	+12.0	4.0
C. G.	27	164.5	99.6	+ 65.9	69	246	251	177	182	41.5	41.5	± 0.0	23.4	22.8	+ 2.6	3.5
E. B.	17	157.7	84.8	+ 59.4	90	318	335	228	245	36.4	36.2	+ 0.6	16.0	14.8	+ 8.1	3.5
E. B.	17	157.7	83.4	+ 56.8	101	302	326	201	225	46.2	43.8	+ 5.5	23.0	19.5	+17.9	4.0
P. M.	19	165.4	86.0	+ 50.2	79	302	293	223	214	44.6	43.7	+ 2.1	20.0	20.4	— 2.0	10.0
I. B.	21	161.6	85.7	+ 50.0	75	261	267	186	192	47.5	44.6	+ 6.5	25.5	23.2	+ 9.9	8.0
D. M.	24	163.5	85.5	+ 49.2	86	292	283	176	197	51.4	47.8	+ 7.5	29.2	24.3	+20.2	7.0
P. F.	18	159.1	80.7	+ 49.1	69	242	246	173	177	42.3	41.2	+ 2.6	24.5	23.3	+ 5.2	5.0
P. K.	21	161.6	84.2	+ 48.2	60	300	306	240	246	51.0	49.1	+ 3.9	21.2	20.0	+ 6.0	4.0
B. H.	29	159.1	79.0	+ 39.0	80	362	352	282	272	54.6	47.0	+16.2	19.4	17.3	+12.1	4.3
P. M.	19	165.1	78.4	+ 36.9	81	296	296	215	215	44.5	43.0	+ 3.5	20.7	20.0	+ 3.5	10.0
V. C.	21	166.1	79.6	+ 34.6	70	295	324	225	254	51.8	46.6	+11.2	23.0	18.3	+25.7	15.0
K. V.	19	160.5	71.1	+ 30.4	81	321	288	240	207	44.5	38.1	+16.8	18.5	18.4	+ 0.5	13.0
B. H.	23	168.3	72.3	+ 19.5	71	299	305	228	234	42.8	39.9	+ 7.3	18.8	17.0	+10.6	6.0
Aver.	22	159.9	89.0	+ 59.7	85	308	313	224	228	45.4	43.0	+ 5.4	20.8	19.1	+ 8.0	7.1

TABLE 2.—*Difference in Mechanical Efficiency Before and After the Onset of Fatigue in Normal Subjects*

Subject	Age, Years	Height, Cm.	Weight: Kilograms	Weight: Percentage Deviation from Normal	Heat Production per Hour in Calories: Sitting on Ergometer	Exercising with Brake: Before Fatigue	Exercising with Brake: After Fatigue	Energy Spent on Work: Before Fatigue	Energy Spent on Work: After Fatigue	Work Done per Hour Calories: Before Fatigue	Work Done per Hour Calories: After Fatigue	Work Done per Hour Calories: Difference, per Cent	Mechanical Efficiency: Before Fatigue	Mechanical Efficiency: After Fatigue	Mechanical Efficiency: Difference, per Cent	Endurance, minutes
M. A.	22	174.5	72.6	+10.2	75	313	278	238	203	57.2	49.0	+16.7	24.0	24.1	— 0.4	70.0
T. A.	22	158.8	59.7	+ 7.3	63	241	255	178	192	46.0	44.0	+ 4.5	25.8	22.9	+12.7	15.0
M. W.	21	161.3	59.8	+ 7.0	60	316	307	256	247	51.0	45.2	+12.8	19.9	18.3	+ 8.7	29.0
E. S.	18	155.6	55.2	+ 6.5	66	310	296	244	230	50.2	41.8	+20.1	20.6	19.0	+ 8.4	14.0
A. S.	21	160.7	59.3	+ 6.1	87	262	326	175	239	40.3	50.4	—20.0	23.0	21.1	+ 9.0	7.5
R. F.	19	159.4	57.8	+ 6.0	70	313	287	243	217	61.5	46.0	+33.7	25.5	21.2	+20.3	75.0
T. A.	22	159.8	59.0	+ 5.5	59	338	350	279	300	65.0	63.1	+ 3.0	23.3	21.0	+11.0	7.5
J. H.	25	163.2	61.0	+ 4.7	64	365	400	301	336	60.4	63.5	+ 4.6	22.1	18.9	+16.9	4.0
H. W.	27	156.8	57.0	+ 2.8	85	305	278	220	193	49.3	41.0	+20.2	22.4	21.2	+ 5.7	11.0
I. T.	19	158.2	54.8	+ 2.1	77	390	393	313	316	64.3	62.4	+ 3.0	20.5	19.7	+ 4.1	15.0
L. B.	20	165.3	57.8	+ 1.3	65	319	270	254	205	55.2	43.8	+26.0	21.7	21.4	+ 1.4	13.0
M. W.	20	160.7	56.5	+ 1.0	65	250	267	185	202	56.8	40.0	+42.0	30.7	19.8	+55.1	12.0
K. C.	25	164.2	55.8	— 7.0	68	241	317	273	249	57.1	51.3	+11.3	20.9	20.6	+ 1.1	13.5
A. W.	30	160.2	53.2	— 8.6	60	211	225	151	165	47.8	47.0	+ 1.7	31.7	28.5	+11.2	27.0
Aver.	22	161.3	58.5	+ 3.2	69	305	303	236	215	54.9	49.2	+12.8	23.7	21.3	+11.8	22.3

The extraordinarily high average of the normal group was undoubtedly due to the unusually high endurance of M. A. and R. F., being 70 and 75 minutes, respectively.

Owing to the different base line used, the values in this paper cannot well be compared with those published in our previous report.[3] Furthermore, the conclusions of the preliminary report were drawn from too small a number, especially in the case of normal subjects.

TABLE 3.—*Difference in Mechanical Efficiency Before and After the Onset of Fatigue in Underweight Subjects*

Subject	Age, Years	Height, Cm.	Weight		Heat Production per Hour in Calories				Work Done per Hour Calories			Mechan'cal Efficiency			Endurance, minutes
					Sitting on Ergometer	Exercising with Brake		Energy Spent on Work							
			Kilograms	Percentage Deviation from Normal		Before Fatigue	After Fatigue	Before Fatigue	After Fatigue	Before Fatigue	After Fatigue	Difference, per Cent	Before Fatigue	After Fatigue	Difference, per Cent	
M. E.	24	162.6	50.5	—11.9	65	261	265	196	200	49.8	50.0	— 0.4	25.4	25.0	+ 1.6	10.0
M. F.	24	162.2	50.1	—12.5	57	238	263	181	206	48.1	48.1	± 0.0	26.6	23.3	+14.2	7.0
M. K.	18	163.1	48.0	—14.6	72	239	248	167	176	49.2	44.0	+11.8	29.5	25.0	+18.0	7.0
K. S.	20	156.0	45.5	—14.5	54	299	337	215	282	43.9	41.4	+ 6.0	20.4	14.7	+38.8	6.0
J. L.	23	169.2	50.6	—17.6	60	225	265	166	205	47.0	44.6	+ 5.4	28.3	21.8	+26.1	19.0
C. M.	24	157.2	44.9	—17.7	55	260	270	205	215	35.8	34.8	+ 2.9	17.5	16.2	+ 8.0	28.0
J. O.	23	165.1	48.3	—17.8	63	212	287	149	224	40.7	44.2	— 7.9	27.3	19.7	+38.6	45.0
J. O.	23	165.1	48.2	—17.8	61	221	225	160	164	44.3	42.7	+ 3.7	27.7	26.0	+ 6.5	20.0
R. D.	24	156.6	44.3	—18.1	66	258	214	192	148	54.7	45.5	+20.2	28.5	30.7	— 7.2	8.0
M. K.	21	164.1	46.9	—19.3	65	217	225	152	160	46.6	44.7	+ 4.2	30.7	27.9	+10.0	8.5
V. S.	22	154.9	42.2	—20.7	72	208	248	136	176	40.3	50.1	—19.6	29.6	28.5	+ 3.9	14.0
M. C.	25	158.9	40.8	—27.0	52	258	250	206	198	47.5	46.3	+ 2.6	23.1	23.4	— 1.2	14.0
M. N.	22	152.4	38.0	—27.4	52	255	230	203	178	39.7	32.9	+20.7	19.6	18.5	+ 5.9	14.0
Aver.	23	160.7	46.0	—18.2	61	240	256	179	195	45.2	43.8	+ 3.8	25.7	23.1	+12.6	15.4

SUMMARY

A total of forty-eight experiments were conducted on thirteen obese, fourteen normal and eleven underweight women ranging in age from 16 to 30 years.

As was shown in our previous paper,[3] the obese had a lower mechanical efficiency than the normal or underweight subjects. The indications are that an increase of obesity is accompanied by a decrease in mechanical efficiency.

With the exception of six of forty-eight experiments, the mechanical efficiency was lower after the onset of fatigue than before.

The amount of work done per hour was likewise decreased after the onset of fatigue.

A wide variation in endurance of work was found in all the three groups, but the average value was the lowest in the obese and the highest in the normal subjects.

3. Wang, Chi Che; Strouse, Solomon, and Smith, Edith A.: Influence of Fatigue on the Heat Production During Muscular Work in Obese, Normal and Thin Subjects, J. Biol. Chem. **74**:38 (April) 1927.

Book Reviews

PRAKTISCHE DIFFERENTIALDIAGNOSTIK FÜR AERZTE UND STUDIERENDE. Herausgegeben von Professor Dr. Georg Honigmann. Band VI: Haut-und Geschlechtskrankheiten. Teil 1: Differentialdiagnostik der Hautkrankheiten. Von P. Tachau. Price, 13 marks. Dresden: Theodor Steinkopff, 1929.

In this book "A Practical Differential Diagnosis of Diseases of the Skin and Genitals for Physicians and Students" by Dr. Paul Tachau, given by Dr. Georg Honigmann-Giessen, there is a lucid and concise differentiation of all skin and genital lesions which could in any way be similar to syphilis, gonorrhea, soft ulcer and granuloma inguinale. This treatise infers that the specialties of dermatology and venereology go hand in hand. No attempt is made to discuss treatment; as the title states, all emphasis is placed on the diagnosis of the various conditions.

The old Ricord division into primary, secondary and tertiary stages of syphilis has a practical value but no sharp limits in regard to the length of time the stages should be taught. Secondary manifestations are most frequent in the first year after the infection and tertiary signs commonly occur later. Parenchymatous nervous syphilis, malignant syphilis and congenital syphilis are briefly but adequately discussed.

In doing a dark-field examination for *Spirochaeta pallida*, a bloody serum should be avoided; more use of the puncture of ulcer bases is recommended; an intensive source of light is emphasized. The culture of spirochetes is not yet serviceable. Repeated examinations are urged.

It should be kept in the foreground that serology gives the clinician only the objective results of laboratory experiments. The Wassermann reaction is not an office procedure, but every physician should understand its performance. Positive Wassermann reactions are occasionally obtained in frambesia, recurrent fever, trypanosomiasis, tropical ulcer, leprosy, malaria, scarlet fever, lupus erythematosis, soft ulcer and after narcosis. In evident discrepancies, serologic examination must always be repeated. The Wassermann reaction becomes positive at the earliest three and one-half weeks after the infection. A positive reaction is almost always found in the secondary stage, except in malignant syphilis in which the serum reaction is often negative. In tabes dorsalis there is obtained from 60 to 80 per cent positive reactions; in paralysis, about 100 per cent. There is no discussion of the Kahn or similar reactions.

The luetin reaction has a diagnostic importance in tertiary and congenital syphilis; it is used also to differentiate cerebrospinal syphilis and paralysis.

An examination of the cerebrospinal fluid has the greatest practical importance in the differential diagnosis of syphilis and the control of therapy; so, it should never be omitted in any case of syphilis. Its pressure, pleocytosis, albumin, globulin, colloidal gold curve, Wassermann and precipitation reactions should be noted. All examinations of the spinal fluid should be carefully correlated with the clinical observations; in case of doubt, the fluid examinations should always be repeated. Positive fluid observations after the first year of infection are of substantial importance as far as indicating probable nervous syphilis.

In the discussion of acquired syphilis it is worthy of note that a differentiation is stressed between initial sclerosis and the true chancre as commonly pictured. Any infiltrated area of the genitals must be differentiated from syphilis. It is also believed that the spirochetes can enter the body without leaving a typical lesion at their point of entrance. Linear chancres are not uncommon.

Syphilitic reinfection in the presence of already existing syphilis is uncommon. One should always be on the lookout for extragenital chancres. The earliest the serum reaction will become positive with extragenital lesions is in the sixth or seventh week after infection.

There are excellent differential diagnostic discussions of genital and extragenital primary lesions, secondary skin and mucous membrane manifestations. Hair and nail changes are mentioned. The symptoms of syphilis of each body system are included. In differentiating tertiary syphilids one must not mistake a penile tertiary nodule (chancre redux) for a true chancre.

Congenital syphilis always implies a syphilitic infection of the mother. Germinative transmission of syphilis is improbable. The use of tact in obtaining histories is suggested.

All patients with syphilis should be watched for from three to five years. Wassermann reactions should be tried quarterly the first year, semi-annually the second year and annually thereafter. All cures must undergo a lumbar puncture. Long supervision and careful study of children suspected of syphilis are recommended.

Gonorrhea is the most frequent disease of the genital organs. For diagnosis of fresh cases the methylene blue stain of the discharge is used; in old, treated and suspicious cases a Gram stain is carefully done. The culture work of gonorrhea is considered impracticable for clinical use. Immunity reactions have no great importance in the differential diagnosis of gonorrhea.

Many American workers could profit by reading the excellent discussion of nonspecific urethritis. It should be noted that a nonspecific urethritis rarely has posterior complications. The Germans make much use of the two glass urine test in following the course of a urethritis. Prostatitis of any grade should be treated until absolutely cured. Functional disturbances of overtreated urethras should be avoided. Generative impotencies are differentiated from coital impotencies.

Clinical symptoms of gonorrhea in the female are few and often go unnoticed and undiagnosed. The gonorrheic macule or flea bite appearance of a duct of a Bartholin gland almost always speaks for gonorrhea. Vulvovaginitis in small girls should be guarded against.

The most frequent site of extragenital gonorrhea is the rectum and is especially noted in women and girls. Gonorrheal conjunctivitis comes next in order of frequency. Gonorrhea of the oral cavity occurs rarely in the new-born infant.

Of metastatic gonorrhea, arthritis is common and is rare in women. One must always keep in mind the gonorrheal skin diseases as manifested by scarlatiniform, multiform, erythematous, nodular and hyperkeratotic changes.

The differential diagnosis of soft ulcer depends on finding the streptobacillus of Unna Ducrey. Its fishlike arrangement and inability to take the Gram stain are quite characteristic. Skin reactions with streptobacillus vaccine serve as valuable diagnostic aids. Dark-field examinations should be done repeatedly on all genital lesions.

In the discussion of granuloma inguinale no mention is made of Donovan's bodies. This is a rare lesion in Germany.

The author appends twelve tables of very good illustrations to aid in emphasizing the differential characteristics of lesions.

This treatise is an excellent concise summary of syphilis from a diagnostic standpoint.

LECCIONES DE CLINICA MEDICA, 1926-1928. By PEDRO ESCUDERO. Volume IV. Buenos Aires: Pedro Garcia, 1929.

The fourth volume of the annual publication of the Escudero Clinic at Buenos Aires maintains the high standard of the previous volumes that have been reviewed in these pages. It is an imposing tome of 600 pages, this one not having the usual large quota of illustrations.

There are twenty-two separate communications, almost all of them this year falling under the head of cardiovascular disease. While there is comparatively little original research work reported, there are the usual painstaking studies in the clinic and laboratory of a series of unusual cases which often throw important

new light on disease. This is especially true of the series of studies on the arrhythmias. These interesting conditions were investigated thoroughly with all modern means, and the results of treatment, especially with quinidine or digitalis, are elaborately illustrated with electrocardiograms and pulse tracings. The chart on page 97 demonstrates by electrocardiogram the points of origin of the various arrhythmias and is illuminating.

While space does not permit a detailed review of this material, a few interesting points may be noted. The so-called thyroid heart was investigated painstakingly and the conclusion arrived at that medical management of such cases is worse than useless. Rest, diet and the usual medication have no effect on such cases of delirium cordis, but the only therapeutic measure of any value is thyroidectomy, that is, the removal of the thyrotoxicosis and, according to Escudero's experience, such cases stand the operation very well and the benefit is prompt and lasting. Escudero believes that a good many such cases are unrecognized and that there exists a group in which the thyrotoxicosis manifests itself clinically principally in the heart, and warns against overlooking the etiology of the condition.

Another interesting point the author makes is the failure of the roentgen ray to demonstrate the pathology in most cases of aortitis. He believes that outside of the existence of the actual aneurysm roentgenograms are deceiving. Neither the slight amount of increased density nor the slight amount of dilatation present in such cases is capable of being demonstrated in the x-ray picture, and he warns against making such diagnoses on roentgen evidence alone.

THE MEDICAL MUSEUM, MODERN DEVELOPMENTS, ORGANIZATION AND TECHNICAL METHODS, BASED ON A NEW SYSTEM OF VISUAL TEACHING. By S. H. DAUKES, O.B.E., M.D., D.P.H., D.T.M.&H., Director of the Wellcome Museum of Medical Science. Cloth. Pp. 181, with illustrations. London: The Wellcome Foundation, Ltd., 1929.

We are all too familiar with the usual type of medical museum, composed in the main of collections of pathologic and anatomic material, a few wax models and various objects of medical interest of a bygone age. They have not kept pace with clinical and therapeutic advances. In many the labels are inaccurate or incomplete, the catalogs are out of date, and the specimens are in a bad state of preservation, little attention having been paid to systematic arrangement or easy reference.

"A system which links up the various branches of medical work as one demonstration, providing a display which may be fittingly termed 'synoptical' . . ." was the original conception of the founders of this new type of museum, herein described, in order to fulfil certain desirable objectives: (1) collection and preservation of material, (2) reference, (3) research, (4) education (specific teaching) and (5) education (general teaching for the public).

During the World War, the author was responsible for the organization and administration of the School of Army Hygiene at Leeds. Intensive courses were given and were made possible only by the development of "demonstration centres," in which actual conditions to be met were faithfully reproduced, the study of various problems being taken up in a practical manner and further amplified graphically by the free use of paintings, photographs, labels, plaster and wax models, etc. The unusual success of this venture furnished the idea for a new type of museum for teaching purposes.

A complete revision and expansion of the then existing Wellcome Museum of Tropical Medicine and Hygiene provided a nucleus for the present development, to which type medical museums of the future will probably conform. To quote further, "In such a museum, there can be no finality — progress is the essence of its existence; indeed, in every type of museum, it is essential to keep up to date."

Special chapters are devoted to method, arrangement, preservation of material, labeling and catologing. There are many excellent illustrations and an extensive bibliography.

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When you prescribe for a diabetic patient keep in mind the efficacy of Knox Gelatine as an agent for satisfying appetite without violating the most rigid protein diet.

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Recognized dietetic authorities have prepared dishes made with Knox Sparkling Gelatine that are a real contribution to the successful treatment of diabetes. Here are two recipes that will aid you in giving diabetic patients complete instructions for home co-operation with your treatment.

KNOX *is the real* GELATINE

Contains No Sugar

JELLIED VEGETABLE SALAD (*Six Servings*)

	Grams	Prot.	Fat	Carb.	Cal
1 tablespoon Knox Sparkling Gelatine	7	6	—	—	—
¼ cup cold water, 1½ cups hot water	—	—	—	—	—
1 teaspoonful whole mixed spices	—	—	—	—	—
½ teaspoon salt, ¼ cup vinegar	—	—	—	—	—
½ cup chopped cabbage	50	1	—	3	—
½ cup chopped celery	40	1	—	2	—
½ cup canned green peas	40	1	—	4	—
¼ cup cooked beets, cubed	40	1	—	3	—
Total		10	—	12	88
One serving		2		2	15

Soak gelatine in cold water for five minutes. Bring to boil water, salt and spices. Pour on gelatine to dissolve it and add vinegar. When jelly is nearly set, stir in the vegetables, pour into mold and chill until firm. Unmold on lettuce and serve with salad dressing. Garnish with sprig of parsley or strip of pimento.

JELLIED CHICKEN IN CREAM (*Six Servings*)

	Grams	Prot.	Fat	Carb.	Cal
1 tablespoonful Knox Gelatine	7	6	—	—	—
¼ cup cold chicken broth or water	—	—	—	—	—
1¼ cups boiling chicken broth, fat free	—	—	—	—	—
½ teaspoon salt	—	—	—	—	—
Pinch pepper	—	—	—	—	—
1 cup cooked chicken, cubed	125	24	20	—	—
¼ cup cream, whipped	55	1	22	1.5	—
Total		31	44	1.5	526
One serving		5	7	—	88

Soak gelatine in cold liquid for five minutes and dissolve in hot broth. Season with salt and pepper and chill until nearly set. Fold in chicken and whipped cream. Turn into molds and chill until firm. Serve on lettuce or garnish with parsley and strip of pimento.

If you agree that recipes like the ones on this page will be helpful in your diabetic practice, write for our complete Diabetic Recipe Book—it contains dozens of valuable recommendations. We shall be glad to mail you as many copies as you desire. Knox Gelatine Laboratories, 451 Knox Ave., Johnstown, N. Y.

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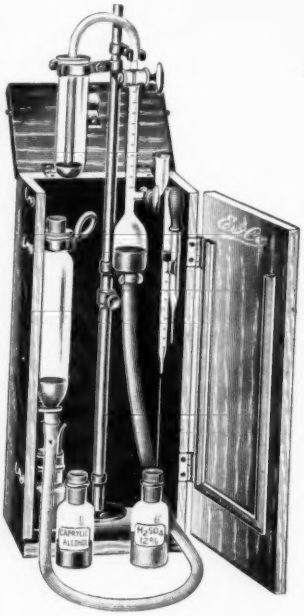

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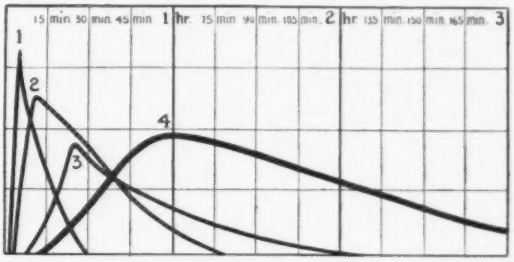

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